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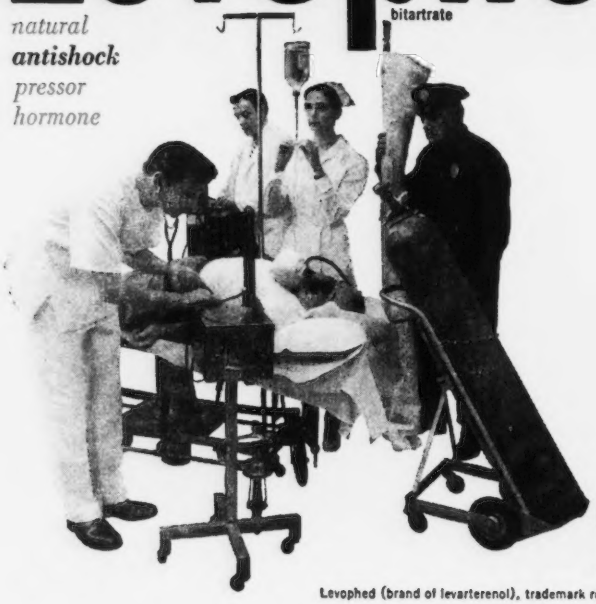

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Editorial

Cardiovascular Research in Russia

THE RUSSIAN tradition in medical-biological research is proud and long. It can be traced back to the foundation of the Russian Imperial Academy of Sciences by Catherine I (1725). Until the first World War, many important Russian medical and physiological papers were published abroad, mostly in French and German periodicals. Even in the early twenties quite a few Russian papers were published in German periodicals. This stopped gradually, and now papers by Russian authors (such as Miasnikov's article[1]) in foreign journals are rare. The communications of Russian participants in international medical meetings also are usually given in Russian. Therefore, information about Russian medical research, available to the average worker outside Russia, is limited to abstracts. This impediment is a semipermeable membrane rather than an "iron curtain." Most of the leading Russian authors are quite well informed about the recent Western literature; for instance, in a recent review[2] Miasnikov and Ratner compared research on essential hypertension inside and outside Russia. It is fair to assume that the Russian medical libraries are well supplied with current Western periodicals, and that no significant barrier of language exists in Russia. This situation is disadvantageous to the American research worker. A large-scale translating and reviewing program has been initiated at the National Institutes of Health in Washington. Political influences probably account for publication of Russian authors nearly exclusively in Russian journals. Perhaps, it is to be expected that Russian, by the weight of the publications, will ultimately develop to the level of an international scientific language. There is also a definite tendency to assign priority for important medical discoveries, far back into the nineteenth century, to Russian authors. Internationally used Latin anatomic terms, for instance jugular or portal veins, carotid or temporal arteries, are replaced by Russian names, but they are not listed in most of the available Russian dictionaries. Sometimes, anatomic structures are named after Russian authors, for instance, one of the cardiac nerves is called "Pavlov's nerve," and cannot be identified in the Western anatomic literature. There is an appreciable, and apparently increasing number of publications in Russian of Czech, Hungarian, Rumanian, Polish, and East-German authors.

My impressions on Russian cardiovascular work are based essentially on the literature read in preparation of 2 recent reviews[3, 4] (about 1,000 papers). The emphasis in research is clearly on the central nervous system, a large part of the cardiovascular research is concerned with the effect of the central and autonomic nervous system on cardiovascular functions. Less than 10 per cent of the papers published in the Fiziologicheskii Zhurnal SSSR are concerned with cardiovascular aspects; since this is the only Russian physiologic periodical, it should reflect the general trend of physiologic research. There is no periodical in Russia devoted to cardio-

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vascular physiology and pathology like Circulation, Circulation Research, British Heart Journal, Zeitschrift für Kreislaufforschung, Cardiologia, etc. In contrast there are periodicals for very many other specific medical fields, such as otolaryngology, obstetrics, pediatrics, ophthalmology, neurosurgery, physiology of visceral receptors, neuropathology, etc. Curiously enough, there is a reviewing journal of Western cardiovascular literature published in Russia.

Consequently, the Russian cardiovascular literature is scattered over a large number of Russian medical periodicals. Furthermore, a rather large part of the Russian cardiovascular literature does not appear in periodicals, but is published in volumes which are issued in irregular sequence from the large medical institutions, such as the "Pavlov" Institute of Physiology in Leningrad, the Academy of Medical Sciences in Moscow, the Grusinian Heart Research Institute. Since these volumes are not systematically indexed, it is difficult outside Russia to know in time of their appearance and to prepare any adequate review of Russian medical literature without cooperation of Russian authors. That such cooperation is usually gladly given, is one of the encouraging signs of international scientific cooperation.

When I started preparations for my review on "Russian Physiology—Cardiovascular Aspects,"[3] I wrote to Professor K. M. Bykov, member of the Academy of Sciences, who may be regarded as the Dean of Russian physiologists, asking him for his help in obtaining information, particularly for a list of important papers. A translation of his letter may be of interest:

"In view of the importance of your work in the preparation of the review on cardiovascular physiology, I hasten to fulfill your request. I am sending you a list of the recent fundamental papers of Soviet scientists on the problems in the line of your interest. This list is far from complete, and does not pretend to give even adequate partial information on the field of cardiovascular physiology, but it contains nearly all really fundamental papers. This list has been prepared in the Library of the Academy of Sciences of U.S.S.R., which will, in the near future, send you if not all, in any case the larger part of these papers. Several reprints are enclosed in this letter.

"I shall be very happy if our help in the selection of literature will contribute for the further strengthening of scientific and cultural ties between the people of the world."

The list of 32 papers shows clearly the different approach and different emphasis of cardiovascular research in the United States and in Russia. A detailed listing of this bibliography would exceed the scope of an editorial. It is of interest that 20 of the 32 papers are concerned with cardiovascular reflexes and central nervous regulation of circulation.

The emphasis on central nervous regulations in any field of medicine and physiology goes back to I. P. Pavlov, who suggested that the central nervous system, particularly the cerebral cortex, controls the activity of all internal organs. Pavlov's original work on conditioned reflexes, essentially limited to the salivary and gastric secretion, has been considerably enlarged and expanded, mainly by Bykov and his associates. They obtained conditioned reflexes of various autonomic (including cardiovascular) functions, which changed in various types of pathology. Lesions of the cerebral cortex were found to affect the development of experimental pathology.

Pavlov's concept of the dominating importance of the cerebral cortex is today generally accepted in U.S.S.R. to a degree which is hard to visualize from outside. There is hardly a medical paper without some reference to Pavlov, sometimes going back as far as 1882. In Chernogorov's monograph[5] on angina pectoris, Pavlov is quoted more frequently than any cardiologist, and even in Dekhtar's[6] textbook on electrocardiography Pavlov is frequently quoted, although he never worked in this field. Over 400 papers on Pavlov published from 1949 to 1952, and 335 papers from March 1953 to April 1954 are listed in 2 editorials of the Fiziologischeskii Zhurnal SSSR.[7, 8] This bibliography includes articles of the most prominent authors in physiology

neurology, surgery, ophthalmology, etc., attempting to show the importance of Pavlov for the various fields of medicine. Physiology in U.S.S.R. is now in general called "Pavlovian Physiology." Thus, a large, if not the largest, part of Russian research in medicine is undertaken in order to prove and to verify the validity of Pavlov's concept. Arterial hypertension, ("Hypertensive Disease") for instance, is considered to be a cardiovascular neurosis, brought about by dysfunction of the cerebral cortex through emotional trauma. G. F. Lang[9] is credited with being the first author to present a thorough documentation of a neurogenic theory of pathogenesis of essential hypertension. Another example is angina pectoris; the role of the cerebral cortex is considered to be as important as the state of the coronary arteries.[5]

In the attempt to prove the validity of Pavlov's concept for cardiovascular disease, experimental studies were carried out on an unprecedented scale. Important results were obtained which are not only of theoretical interest, but have found also therapeutic application, such as the sleep therapy in essential hypertension.

It must be surprising to any investigator that all recent experimental work in Russia tends to support Pavlov's concept; it is quite unusual that all results turn out as expected. The controversy in Russia is essentially limited to secondary, though not unimportant questions, such as the finer mechanisms and pathways of nervous cardiovascular regulations.

Regarding essential hypertension, all Russian authors agree that central nervous involvement is secondary, but there is some discussion about the time, course, and mechanism of renal involvement.

Perhaps, Russian authors will maintain that Pavlov's concept as a guiding principle is superior to other hypotheses. However, some other broader aspects may be involved in the different approach of Western and Russian cardiologists, that were lucidly discussed by E. G. Boring in Chapter 16, "Concerning Scientific Progress" of his book, "Sensation and Perception in the History of Experimental Psychology" (New York, 1942). Boring attached much significance to the factors limiting scientific progress, which are illustrated with examples from the history of exploration of the psychophysiology of sensation and perception:

> "1. Scientific progress at any point waits on the discovery in instruments and technics."
>
> "2. Discovery is serial; it presupposes other knowledge."
>
> "3. Insight conforms to the Zeitgeist, only rarely does it depart widely from contemporary thought."
>
> "4. Individual thinking also shows its inertia; men do not readily perceive the obvious when it contradicts their habits of thought."
>
> "5. Personal attitudes constrain or divert thought."
>
> "6. Social attitudes also constrain thought. Here we have the influence of the schools . . . The in-group magnify their agreements and rise to repel, or at least to depreciate, the out-group . . . Within the school agreement is facilitated . . . Laboratory atmosphere largely determined what would be found in answer to (a) question, and laboratory atmosphere often extended from a parent laboratory to its offspring . . . There can be no doubt that within the Zeitgeist there are local Geister which determine what theory you shall apply to your experimental findings or even how you shall record your data."

Boring did not have Russian experimental work in mind, but items 3, 4, and particularly 6 appear to be quite pertinent. It seems that a different Zeitgeist has developed in Russia on the basis of a different social structure, facilitating the melting of all preexistent individual schools of thought into a unified, single school of thought on a tremendous scale. That many important positions in experimental medicine in Russia in the past 2 decades were or are held by former associates of Pavlov was undoubtedly a contributing factor. Pavlov's concept has stimulated research related

to nervous regulation on a large-scale delaying progress in other areas of cardiovascular physiology and pathology, for instance, the development of new methods. At the same time, it is encouraging that important results can still be obtained with older simple methods. However, there are recent signs of catching up in technic; ballistocardiography, vectorcardiography, and the V leads are in the phase of introduction. On the other hand, the search for electrocardiographic leads with minimal distortion, which characterizes the recent Western progress in electrocardiographic theory, has no counterpart in Russia. I also have not noticed studies with intracellular recording from myocardial fibers. These are only a few examples to characterize the slow development of technic, but there are also notable exceptions, such as Kedrov and Naumenko's[10] excellent work on cerebral circulation, direct visual observation of coronary or pulmonary circulation by means of thoracic windows (Sinitsyn, Bekauri et al, quoted in 3), etc.

Evaluation of statistical reliability is rare, and often the published data are insufficient for interpretation of statistical and biologic significance. One of the most interesting and important results is the production of arterial hypertension and coronary insufficiency in monkeys by means of experimental neurosis (Miminoshvili, Magakian, and Kokaia[11]), but the authors do not give information about the incidence. Probably, not all neurotic animals developed coronary insufficiency; the important question whether this is a minority or majority remains open, although the authors could easily have provided that information.

In a mutual exchange of information, we are, of course, primarily interested in areas where Russian research is advanced. In addition to nervous cardiovascular regulations, cardiovascular resuscitation has been extensively studied. One of the most powerful procedures, developed by Negovskii,[12] is centripetal intra-arterial injection of comparatively small volumes of blood, which has found large clinical application. Considerable work has been done on ontogenetic development of cardiovascular functions from intrauterine phases to the adult stage, but the volume of Russian research on aging of cardiovascular functions (i.e., from the adult stage to senility) lags considerably behind that in the Western cardiologic literature.

The important question arises how far the Russian results, particularly in so subtle an area as the regulatory influence of the cerebral cortex, can be reproduced in Western laboratories, with use of different methods of recording, and without or with little influence by anticipation of results in the line of Pavlov's concepts. There is no objective reason to doubt the honesty and accuracy of the work of Russian authors, but the limitations of habit and schools of thinking, as stated by Boring, apply to the Russian as well as to other societies. Certainly, many of the Russian results are important enough to warrant large scale re-investigation.

This article is written in the hope of ultimate cooperation with Russian cardiologists, as also expressed in Bykov's letter. Ultimate cooperation, of course, is not possible without frank mutual criticism. As an example of Russian criticism of American work, we refer to D. A. Biriukov's report on the 19th International Physiological Congress in Montreal (1953) published in the Fiziolog. Zhurnal SSSR Vol. 50: 129-136, 1954. Biriukov is the editor of this journal. The translated selections of Biriukov's report are printed in italics. *Since out of the two thousand members attending the meeting, twelve hundred were from the United States and four hundred from Canada, the Soviet members of the Congress felt they had full opportunity to appraise the present state of physiological research in U.S.A. (p. 129, paragraph 1).*

(In view of the high percentage of cardiovascular studies presented at the Congress by American authors, Biriukov's criticism applies largely to cardiovascular research.)

While acknowledging the high level of technic and methods, Biriukov deplores the paucity of ideas in the work of the American physiologists. *"The topics of their investigations are, as a rule, trivial. The overwhelm-*

ing majority (of American studies) do not open further perspectives for research and cannot grow to the level of original fundamental scientific problems. In the absence of a correct methodological basis, these investigations are limited to purely empiric explorations" (p. 130, paragraph 6).

"It was up to the Soviet delegation to discuss the fundamental physiological problems and to show approaches for their solution" (p. 130, par. 7/8)."

The absence of consideration of Pavlov's concepts is deplored, and several authors are severely criticized because of "anti-Pavlovian" tendencies. Obviously Biriukov and, in general, the Russian scientists would like to see world-wide acceptance of Pavlov's concepts. This would mean a world-wide uniformity of thought, approach, and interpretation such as prevails in Russia. In the long run, universal acceptance of any single concept, Pavlov's or that of any other great physiologist would inhibit scientific progress, for controversy between different theories is one of its elemental sources.

Biriukov also objects to cardiac catheterization in man because *it exceeds the limits set by ethical and humanitarian considerations.* With the wide diagnostic application of cardiac catheterization in all larger American hospitals without which the spectacular recent advance of cardiac surgery would have been impossible, Biriukov's opinion sounds strange, but it may help to explain the relatively slow development of Russian cardiology in these important areas.

The earnest desire of American and Russian authors for closer contact and cooperation is one of the most encouraging features. Since the main experimental effort has been made in a different direction, both sides would have much to gain. However, cooperation is possible only by mutual respect of opinions, even when different in fundamental concepts. Conflict of opinions to be clarified by experimental work would be the most powerful source for further advance. Obviously, both sides have to be open-minded for mutual understanding.

In conclusion we would like to refer to one of the great Russian physiologists, A. A. Ukhtomskii, whose work is much too little known outside Russia. In his paper on fatigue read at the 1934 meeting of the Russian Physiological Society, he pointed out that there are two types of research work; the first type, which is the more frequent, shows results in the line of expectation, filling out gaps of information. Important as this is, the real progress is made by the second type of studies, with results outside the line of expectation.

ERNST SIMONSON

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Anomalous Drainage of Entire Pulmonary Venous System into Left Innominate Vein

Clinical and Surgical Considerations

By DENTON A. COOLEY, M.D., AND HAROLD A. COLLINS, M.D.

Total anomalous drainage of pulmonary venous blood produces a severe circulatory disturbance. In the most common type of this category of lesions, the entire venous return from the lungs enters a common venous channel ascending in the left superior mediastinum where it connects with the innominate vein. Seven cases of this type are described. Successful total correction was possible in 4 of these patients in whom a special technic was used, which incorporated the pump oxygenator for temporary cardiopulmonary bypass. This technic provides optimum conditions for complete correction of this complicated anomaly.

RECENT increased interest in open heart surgery has revealed that anomalies of pulmonary venous drainage are much more common than previously realized. Interestingly enough, Winslow[1] first described anomalous connection of the pulmonary veins of 1 lung more than 200 years ago (1739) and in 1798 Wilson[2] recorded a case of total anomalous drainage of pulmonary veins into the systemic venous circulation. At present it is recognized that anomalous drainage of a portion of one or both lungs is relatively common and frequently accompanies atrial septal defect. Hemodynamic effects of the partial anomaly are generally well tolerated and, depending upon the extent of the anomaly, may be compatible with an asymptomatic state. Total anomalous drainage of pulmonary veins is less frequently encountered and usually is associated with greater morbidity and poor prognosis. For example, in a review of the reported cases Healey[3] discovered an average age at death of 1.8 years in total anomalous pulmonary venous drainage. This fact emphasizes the need for early recognition of the lesion in infants, control of cardiac decompensation, and surgical correction of the lesion. The purpose of this paper is to present certain observations based upon clinical experience with 7 cases of total anomalous pulmonary venous drainage into the left innominate vein and the details of successful surgical management in the last 4 consecutive cases.

Complete anomalous pulmonary venous drainage occurs in several anatomic forms. Common to all forms, however, is the fact that the pulmonary veins from both lungs usually converge to form a chamber or confluence posterior to the left atrium. Most frequently a single anomalous vein emerges from this chamber to join the systemic venous circulation. In a classification based upon the level of emptying of this anomalous vein into the systemic venous circulation Darling and co-workers[4] have recognized 4 types of total anomalous pulmonary venous connections. 1. Supracardiac level: In this type the anomalous connection is usually made with the left innominate vein through a remnant of the left superior vena cava extending superiorly from the common pulmonary venous trunk. This is the anomaly with which this paper is concerned (fig. 1). Infrequently direct connection to the right superior vena cava may occur. 2. Cardiac level: Total drainage occurs in this type with connection into the right atrial cavity directly or into the coronary sinus, which in turn enters the atrium at the usual site but with a greatly enlarged

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ostium. 3. Infracardiac level: In this type, drainage from the posterior chamber occurs into the systemic venous circulation through an anomalous vein extending below the diaphragm. Pulmonary venous blood returns to the right atrium via the inferior caval system. 4. Combined type: In this type, connection may be made independently at 2 or more levels with total drainage into the right atrium by multiple channels. Occasionally extensive abnormalities in systemic venous drainage are also present.

Of the various types of total anomalous pulmonary venous drainage the most common appears to be supracardiac (type 1) with connection via a remnant of the left superior vena cava (fig. 1). Keith and associates[5] in a survey of reported cases found 43 per cent to be of this type.

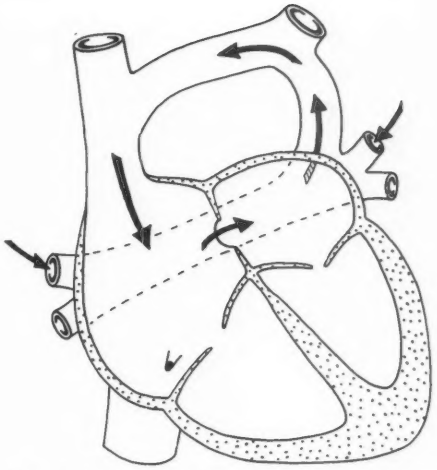


FIG. 1. Drawing showing total anomalous venous drainage into left innominate vein and the usual associated patent foramen ovale.

Embryologically the lungs are derived from the foregut with which they share a common blood supply. In early stages the pulmonary veins are derived from the splanchnic plexus and have multiple communications with 2 systems, the cardinal system of veins and the umbilicovitelline system. From the cardinal system the superior vena cava, innominate veins, and coronary sinus are ultimately derived. In the final stages of development the umbilicovitelline system is represented principally by the portal venous system. In this early stage the primordia of the lungs have no direct connection with the heart. Subsequently a direct connection with the heart occurs as a result of the union of these primary lung veins with an outgrowth from the dorsal wall of the sinoatrial region known as the "common pulmonary vein."[6] After the lungs acquire a route of drainage directly into the heart, the connections between the pulmonary portion of the splanchnic plexus and the cardinal and umbilicovitelline veins are lost. Coincident with the interruption of the main anastomoses of the pulmonary vessels with the umbilicovitelline and cardinal venous systems, the common pulmonary vein and its main tributaries become incorporated into the dorsal wall of the left atrium. With completion of this process the principal venous connection of the lungs is directly with the left atrium and no longer with the systemic and abdominal visceral veins.

According to Edwards[7] the underlying cause in most examples of anomalous pulmonary venous connection is either (1) failure of connection of the atrial portion of the heart with the pulmonary portion of the splanchnic plexus or (2) secondary obliteration of normally developed communications between the atrial portion of the heart and the pulmonary portion of the splanchnic plexus. In either event that portion of the pulmonary tissue that fails to make direct connection with the heart has no route for drainage other than the primitive connection between the splanchnic plexus and the cardinal or umbilicovitelline system of veins. In the most common type of total anomalous pulmonary venous return this communication is through the left cardinal system, which ultimately gives rise to the left innominate vein and the coronary sinus. If a particular portion of the left anterior cardinal vein is not obliterated, it persists as a left superior vena cava and connects the left innominate vein to the coronary sinus.

The left superior vena cava is anatomically in the same position as the anomalous vein

TABLE 1.—*Patients with Total Anomalous Pulmonary Venous Drainage into Left Innominate Vein*

Case no.	Age (yrs.)	Sex	Date of operation	Surgical procedure	Result
1	1/12	F	9-12-55	Anastomosis of vertical anomalous vein to left atrial appendage. Partial ligation of vertical vein	Died 4 hours later
2	2/12	M	2-2-56	Anastomosis of vertical anomalous vein to left atrial appendage. Partial ligation of vertical vein	Died 2 hours later
3	40	M	2-1-57	Exploratory thoracotomy	Died during exploration
4	6/12	M	7-31-57	Complete correction during cardiopulmonary bypass	Excellent
5	4 12	M	1-30-58	Complete correction during cardiopulmonary bypass	Excellent
6	7	M	2-18-58	Complete correction during cardiopulmonary bypass	Excellent
7	8	M	5-29-58	Complete correction during cardiopulmonary bypass	Excellent

connecting the common pulmonary vein to the left innominate vein in cases of supracardiac connection of total anomalous pulmonary venous drainage. This has given rise to the designation of this anomalous vein as a persistent left superior vena cava. According to Edwards and Helmholz[8] this is an incorrect term, since this anomalous vein has no connection with the coronary sinus and it may have a different origin than does the true left superior vena cava. They have suggested the term "vertical anomalous pulmonary vein" to differentiate the two. In some instances, however, this anomaly may be associated with a true left superior vena cava connecting with the coronary sinus (table 1, case 3).

As in other forms of total anomalous drainage a communication exists between the atria (fig. 1). In most cases this communication is either a midatrial septal defect or a patent foramen ovale. The size of the atrial communication may be a factor determining survival although this remains an unsettled question.[4, 9] In addition, a patent ductus arteriosus is frequently present although it is usually of minor physiologic importance. It appears that total anomalous pulmonary venous return without complicating major cardiac defects is twice as common as when multiple cardiovascular anomalies are also present.[5]

The anatomic configuration of the heart in 13 autopsied cases of total anomalous pulmonary venous return was assessed by Keith and associates.[5] The right atrium was 5 to 10 times as large as the left atrial cavity and the right ventricular cavity was 3 to 5 times as large as the left. The circumference of the waist of of the left atrial appendage was usually less than that of the anomalous pulmonary vessel, and orifice of the mitral valve was invariably smaller than that of the tricuspid. Keith stated, "the left auricle is underdeveloped and thus cannot be expected to carry the total blood flow adequately." From a theoretical standpoint he concluded that this anomaly was not anatomically correctible. On the basis of our own experience in which complete correction of this anomaly was accomplished, this conclusion was apparently incorrect.[10] Indeed, from a theoretical consideration this could have been predicted, since the entire cardiac output into the systemic arterial system in these patients depends upon the function of the left ventricle. Thus, the discrepancy in size of the right and left sides of the heart is a reflection only of the difference in volume of

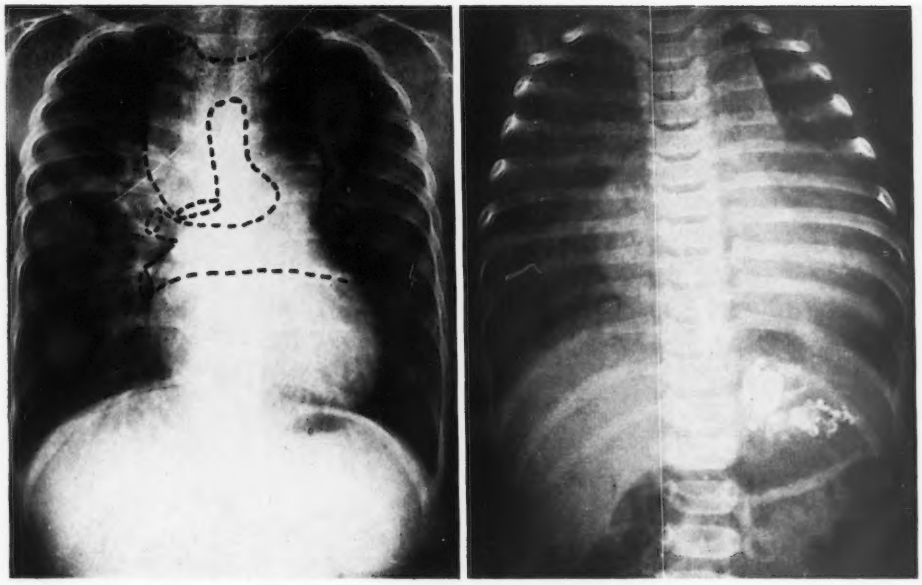


FIG. 2 *Left.* Roentgenogram of chest in child with typical figure-eight mediastinum considered diagnostic of total anomalous pulmonary venous return into left innominate vein (case 7). *Dotted lines* indicate anticipated location of veins.

FIG. 3 *Right.* Roentgenogram of chest in infant with total anomalous venous drainage into left innominate vein (case 4). Film reveals cardiac enlargement and pulmonary congestion but is not diagnostic of the underlying anomaly.

blood being handled on the 2 sides of the heart, and does not represent a true underdevelopment of the left side.

In our experience 2 clinical patterns have been evident in patients with total anomalous pulmonary venous drainage into the innominate vein (table 1). In infants the principal findings are a result of congestive heart failure, whereas in older children the symptoms and findings consist of cyanosis and exertional dyspnea. The magnitude of the right-to-left shunt at the atrial level could explain the 2 patterns. In infants the right-to-left shunt is usually small and the pulmonary arterial flow greatly increased. Thus, cyanosis was minimal. Cardiomegaly, pulmonary edema, hepatomegaly, and distended peripheral veins were manifestations of the cardiac failure. Repeated respiratory infections were common. Emaciation and retardation of growth and development were usually evident.

In contrast to infants, children with this anomaly had dyspnea and increasing fatigue with slight exertion. Syncopal episodes and squatting occurred occasionally. Growth was usually retarded but not to the striking degree noted in infants. Cyanosis and clubbing of the digits were noted. Cardiac size was moderately increased and right ventricular hypertrophy was present. A systolic murmur at the left sternal border was usually audible.

Roentgenograms of the chest in total anomalous pulmonary venous return into the left innominate vein in children reveal an almost pathognomonic cardiac silhouette. These findings were clearly described by Snellen and Albers,[11] who called attention to the figure-of-8 configuration of the mediastinum. The upper half of the 8 is formed by the ascending or vertical anomalous pulmonary vein on the left and the prominence of the distended right superior vena cava (fig. 2). The superior mediastinal vessels pulsate in an "aev" or venous pattern while the pulmonary arterial

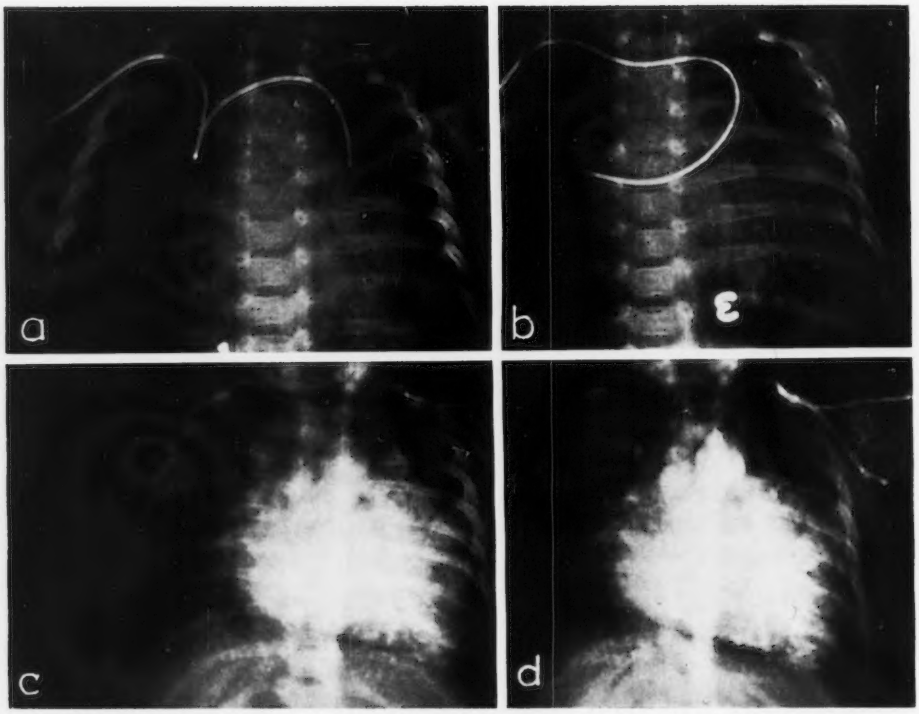


FIG. 4. Roentgenograms made at cardiac catheterization (*a* and *b*) and during angiocardiography (*c* and *d*) in infant with total anomalous pulmonary venous drainage into innominate vein (case 2). The cardiac catheter in (*a*) enters the superior vena cava, left innominate vein, and vertical pulmonary vein and in (*b*) enters the right pulmonary vein. Angiocardiography (*c* and *d*) outlines the superior mediastinal course of drainage of pulmonary venous blood.

pulsation is synchronous with ventricular systole. A hilar dance is usually demonstrable in the pulmonary vessels on fluoroscopy.

Although this roentgenographic appearance is characteristic of the anomaly in children several years of age and older, in infants this pattern is not recognized. In infants cardiac enlargement involving the right ventricle and engorgement of the pulmonary vessels is demonstrated, indicating the presence of a large left-to-right shunt (fig. 3). The superior mediastinal shadow may be widened but the configuration is not at all characteristic of the anomaly. Gott and associates[12] described a box like appearance of the heart with an almost horizontal take-off of the lower border of the heart below the aortic arch. In this age group angiocardiography is useful in delineating the pulmonary venous collecting system (fig. 4). At cardiac catheterization the catheter may be passed into the anomalous venous connection and both lungs may be entered without the catheter entering the heart.

In one of our patients with total anomalous venous drainage (table 1, case 3), a portion of the blood entered the left innominate vein and the remainder entered the coronary sinus (fig. 5*A*). Thus, the typical figure-of-8 appearance was not present, since the vertical pulmonary vein did not carry the entire pulmonary venous return. Cardiac enlargement was extreme, and the anomalous superior mediastinal pulmonary vein was evident (fig. 5*B*). Venous angiocardiography demonstrated the pulmonary venous connection to the left

superior vena cava (fig. 5*C*). The unusual roentgenographic findings in this 40-year-old patient may be explained by the type of total anomalous pulmonary venous return that was present. Although pulmonary venous blood entered the left innominate vein through a vessel anatomically similar to that found in the usual type 1 supracardiac level of drainage (Darling), this case may have been an example of type 2 cardiac level. Thus, it is possible that the patient had predominant drainage to the coronary sinus with a typical persistent left superior vena cava. Nevertheless, the patient is included in this report because of the similarity to the other cases.

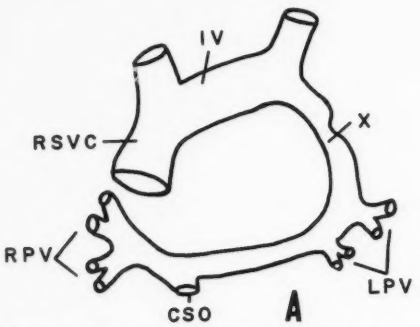


FIG. 5 *A*. Diagram of pulmonary venous system in adult cyanotic patient showing drainage from pulmonary veins into coronary sinus and left innominate vein (case 3). RPV, LPV, right and left pulmonary veins; CSO, coronary sinus ostium; IV, innominate vein; RSVC, right superior vena cava; X, possible persistent left superior vena cava.

Electrocardiograms showed right axis deviation, right ventricular hypertrophy, and an impressive degree of right atrial enlargement.

Cardiac catheterization reveals an increased oxygen saturation of right atrial blood, which is equal to or higher than that of the systemic arterial blood. The demonstration of oxygen saturation in the right side of the heart equal to the saturation in a systemic artery is considered almost diagnostic of total anomalous pulmonary venous drainage[13] (fig. 6). Exploration of the superior caval system with the catheter may reveal the connection of the superior caval system of the pulmonary venous trunk with the left innominate vein (fig. 4). Passage of the catheter through the anomalous channel into both lungs is occasionally possible. The pressure within the right side of the heart and the pulmonary artery is elevated, frequently to a striking degree. Difficulty in entering the left atrium from the superior vena cava was characteristic, since the defects were usually of the foramen ovale type with valvelike mechanism favoring entry from the inferior cava.

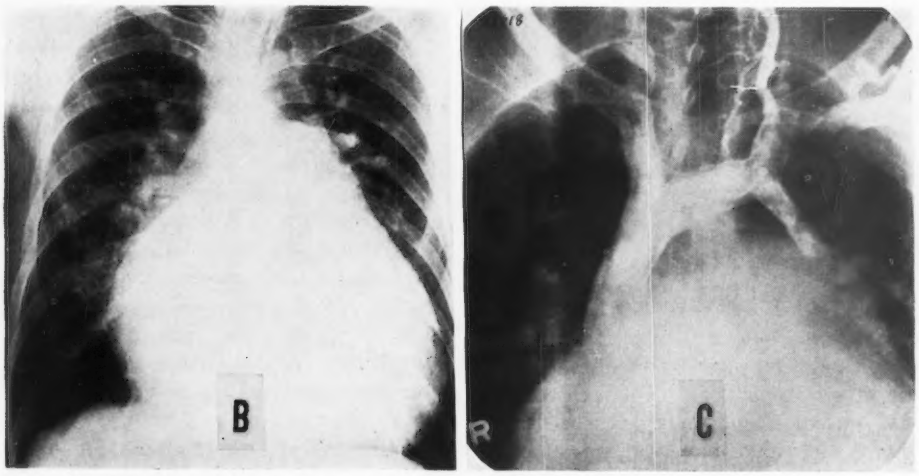


FIG. 5 *B*. Roentgenogram of chest in same patient 5*A* showing extreme cardiac enlargement and pulmonary vascular engorgement. *C*. Angiocardiogram showing anomalous vein entering left innominate vein filled by reflux of contrast material into anomalous vessel.

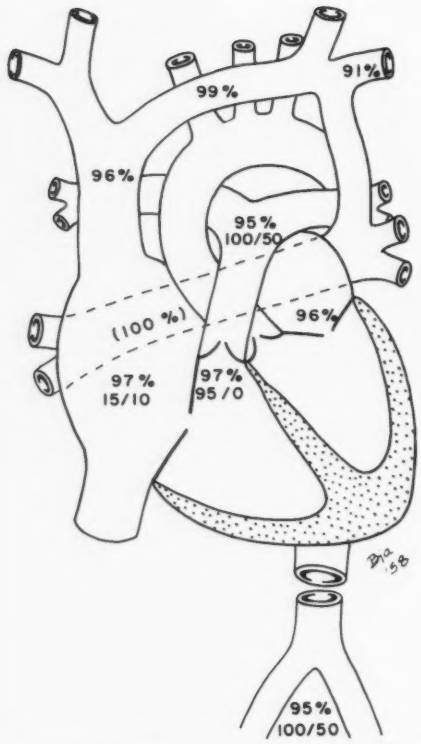


FIG. 6. Diagram showing oxygen saturations and pressures obtained during cardiac catheterization in child (case 7) under general anesthesia and breathing 100 per cent oxygen. Oxygen saturation of blood in right heart identical with saturation in peripheral artery is almost diagnostic of this anomaly.

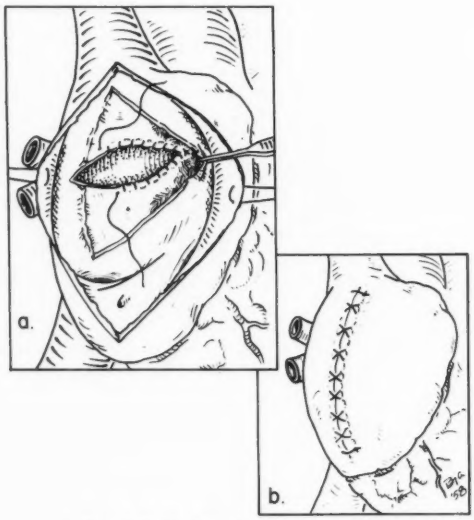
Dye-dilution studies reveal a shorter appearance time from the atrium than from the right ventricle or pulmonary artery. Appearance time from the inferior vena cava is shorter than from the superior cava, demonstrating the preferential shunting of inferior caval blood through the foramen ovale.[13]

SURGICAL TREATMENT

Prior to the development of technics of cardiopulmonary bypass our experience, like that of others, with attempts at complete correction of total anomalous pulmonary venous drainage into the left innominate vein was unsatisfactory.[9, 14-16] In those early surgical attempts an effort was made to perform side-to-side anastomosis between the vertical anomalous pulmonary vein and the small left atrial appendage. Not only was this technically difficult in small infants, but it was also evident that even slight anterior displacement of the dilated heart caused cardiac arrest—possibly due to traction on the atrial septum and constriction of the patent foramen ovale. It was thus evident that a successful technic of repair in infants would be possible only if such manipulation was eliminated. Moreover, in most of these cases the size of the venoatrial anastomosis was inadequate, and complete occlusion of the vertical anomalous pulmonary vein was not tolerated. Partial ligation of this structure was usually the final resort. In these cases no attempt was made to close the atrial septal defect. Senning[17] recently reported successful, complete repair of a total anomalous drainage by a right-sided approach for the atriovenous anastomosis in a 21-year-old patient in whom closure of the atrial defect was accomplished by a closed technic. Ehrenhaft[18] has apparently accomplished a satisfactory repair using hypothermia.

Burroughs and Kirklin,[14] using a pump oxygenator in a 6-month-old infant, attempted side-to-side anastomosis between the common venous trunk and the left atrium from the left side of the mediastinum. A right atriotomy was used to close the atrial septal defect. The patient died 8 hours later in pulmonary edema. On July 31, 1957, we employed for the first time a method of complete correction of this anomaly which fulfills certain important criteria for successful repair.[10] These criteria include (1) use of a pump oxygenator to provide cardiopulmonary function during the cardiac manipulations, (2) creation of the largest possible anastomosis between the common venous trunk and left atrium, (3) closure of the septal defect and enlargement of the left atrial cavity by ventral displacement of the septum, and (4) complete closure of the vertical anomalous pulmonary vein emptying into the left innominate vein.

The surgical technic utilized at present in cases of total anomalous pulmonary venous return into the superior vena cava consists first of exposure of the heart and mediastina



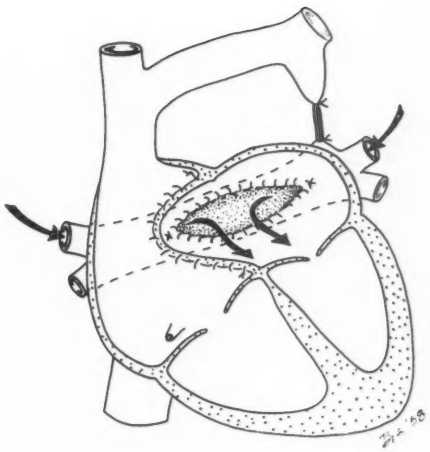


FIG. 7 *Left.* Drawing showing technic of surgical repair of total anomalous venous drainage from the right side using temporary cardiopulmonary bypass. In (*a*) the right atrium is opened widely. The atrial septum is detached posteriorly and retracted with forceps. An ample anastomosis is created between the anomalous vein and the left atrium. The atrial septum is reattached posteriorly and moved laterally to enlarge the left atrial cavity. In (*b*) the atriotomy is repaired. This technic avoids unnecessary cardiac displacement during the repair.

FIG. 8 *Right.* Drawing showing completed repair. The vertical anomalous pulmonary vein is ligated and the left atrial cavity has been enlarged to accommodate the venoatrial anastomosis.

structures through a transverse bilateral thoracotomy transecting the sternum. After incising the pericardium and before any cardiac manipulation, preparations are made for cardiopulmonary bypass. Cannulation is performed of the superior and inferior venae cavae for venous outflow and the femoral artery for return of oxygenated blood by the pump. The vertical anomalous pulmonary vein is temporarily occluded after complete cardiopulmonary bypass is commenced. Actual repair of the anomaly is started by opening widely the right atrium (fig. 7). The atrial communication is identified and the atrial septum is detached from the atrial wall laterally, so that the opening is enlarged. With the left atrium widely opened an ample incision is made parallel to the direction of the common pulmonary vein behind the heart. In order to obtain the largest possible anastomosis the incision is usually continued into the right atrium. Finally a transverse incision is made in the venous trunk and an anastomosis is created between the trunk and the posterior atriotomy (fig. 7*a*). Upon completion of the anastomosis the atrial septum is transposed ventrally and sutured in such manner that the left atrial cavity is increased in size. The right atriotomy is then closed (fig. 7*b*). The final step consists of intrapericardial ligation of the vertical anomalous vein, thus restoring the pulmonary circulation to an essentially normal anatomic state (fig. 8).

CLINICAL EXPERIENCE

A total of 7 patients with total anomalous pulmonary venous drainage into the innominate vein have been treated surgically during the past 3 years (table 1). The first 2 were critically ill infants who were operated upon without a pump oxygenator. In both an anastomosis was created, side to side, between

the pulmonary venous trunk and left atrium or appendage. Partial occlusion of the vertical pulmonary vein by partial ligature was used. Operation in both was poorly tolerated and the patients died in pulmonary edema several hours later. Autopsy revealed a relatively small unsatisfactory anastomosis to an underdeveloped left atrium. Pulmonary edema was apparently produced by the obstruction to venous drainage from the lungs. In neither of these patients was correction of the associated atrial septal defect attempted.

The third patient was intensely cyanotic and in intractable cardiac failure. Extreme cardiomegaly, hepatomegaly, and pulmonary edema were present in this patient whose age of 40 years far exceeded the average life expectancy in this anomaly. Preparations had been made for use of the pump oxygenator, but the patient died during the preliminary exploration and before cannulations could be made. This experience convinced us that preliminary exploration and intracardiac palpation through the atrial appendage should not be attempted in these critically ill patients. Accordingly in all subsequent patients immediately upon opening the chest the cannulations of the superior and inferior venae cavae were done for venous outflow to the pump oxygenator. The common femoral artery was intubated for return of oxygenated blood from the pump oxygenator. Final assessment of the anatomic configuration or arrangement of the anomalies was then accomplished with safety, since cardiopulmonary bypass could be instituted if signs of cardiac distress appeared.

The first successful case of complete correction of total anomalous pulmonary venous drainage has been reported in detail elsewhere. This patient 1 year later is developing satisfactorily and shows progressive improvement. Subsequently 3 more patients have been operated upon with complete correction of the anomaly and all 3 are clinically cured.

Summary

Total anomalous drainage of pulmonary veins is a complicated and serious congenital cardiac anomaly. Usually prognosis is poor, and until recently complete surgical correction was not possible. Drainage of the entire pulmonary venous return into the left innominate vein is the most common type of such anomaly.

Clinical features in 7 patients with this lesion are described. A new method of surgical correction during cardiopulmonary bypass is outlined which provides a complete repair of the defect. In all 4 patients operated upon by this technic a successful result was obtained.

Addendum

Since this paper was submitted 3 more patients with total anomalous pulmonary venous drainage into the left innominate vein have been operated upon successfully by the technic described. Ages of the patients were 6 years, 6 years, and 3 months. In one of the 6-year-old patients an associated pure valvular pulmonic stenosis was treated by open valvotomy at the time of cardiopulmonary bypass.

Summario in Interlingua

Drainage anormal del integre systema pulmono-venose es un complexe e serie anomalia congenite del corde. Usualmente le prognose es pauco promittente, e usque recentemente un complete correction chirurgic non esseva possibile. Drainage a in le sinistre vena innominate es le typo le plus commun de iste anomalia.

Es describite le stato clinic de 7 patientes con iste lesion. Es delineate un nove methodo de correction chirurgic, effectuate con circuition cardiopulmonar e resultante in le complete reparo del defecto. Le technica esseva usate in 4 patientes. Le successo esseva bon in omnes.

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Effects of Periodic Mental Stress on Serum Cholesterol Levels

By Scott M. Grundy, B.S., and A. Clark Griffin, Ph.D.

The effects of academic final examinations on serum cholesterol levels were studied on 2 groups of medical students. A significant increase in the mean total serum cholesterol levels were observed during examination periods as compared to control periods of relaxation. These findings support previous reports of the effects of mental tension on serum cholesterol levels.

DURING recent years many factors have been found that apparently influence the development of atherosclerosis. Factors such as diet, sex, hormonal imbalance, heredity, and exercise are among those being studied most extensively at the present time. There are several recent reports suggesting the possible role of emotional stress as still another factor in atherogenesis and in coronary disease. Friedman, Rosenman, and Carroll[1] have reported increases in serum cholesterols and decreases in blood clotting times in man subjected to cyclic variation of occupational stress. Wertlake and co-workers[2] found evidence that serum cholesterol levels were elevated in students during periods of mental stress associated with examination schedules. In the present paper further studies on the effects of periodic mental stress on serum cholesterol levels have been carried out on a large group of medical students.

Methods and Material

Total serum cholesterol values were determined on groups of freshman medical students as described below. Blood samples were drawn for cholesterol determinations on a group of 50 male students during the middle of the winter quarter of medical school. This procedure was repeated on the same group of students during the first day of final examinations at the end of the winter quarter. Blood samples were again drawn during the middle and at the end of the spring quarter on a group of 47 male students. Comprehensive final examinations were given at the end of the academic quarters. No other examinations were given to these students during the quarters. The ages of the students ranged from 20 to 31 years. Blood samples were collected in the postabsorptive state, and total serum cholesterols were determined by the method of Pearson, Stern, and McGavack.[3]

This work was supported by the Clayton Foundation for Research, Houston, Tex.

Results

Table 1 records the results of this experiment. During control periods in the middle of the 2 quarters mean cholesterol values were 213.0 and 215.7 mg. per cent. Mean values during the final examination periods were 248.2 for the winter quarter and 239.4 mg. per cent for the spring quarter. For both quarters the increase in serum cholesterol during the final examinations was statistically significant ($p < 0.001$). Figure 1 breaks down the total groups into the number of students at examination time showing changes in serum cholesterols of −25 to 0, 0 to +19, +20 to +59, +60 to +89, and +90 mg. per cent as compared to previous levels. During the winter quarter 50 per cent of the students showed an increase greater than 25 mg. per cent at examination time, and 44 per cent of the students had an increase over 25 mg. per cent during the spring quarter. The greatest change in serum cholesterol for a single individual was an increase from 150 to 295 mg. per cent.

Discussion

The exact relationship between elevated serum cholesterol levels and atherogenesis is not understood at the present time. The production of hypercholesterolemia in various experimental animals leads to severe atherosclerosis.[4] The incidence of clinical entities resulting from atherosclerosis appears to be

TABLE 1.—*Changes in Serum Cholesterol Levels during Examination Periods*

Period*	No. of subjects	Mean cholesterol standard error of mean (mg. %)	Mean increase in cholesterol (mg. %)	Percent increase in cholesterol (mg. %)	Significance (p value)
Control I	50	213.0±7.9			
Exam. I	50	248.2±7.9	35.2	16.5	<0.001
Control II	47	215.7±5.4			
Exam. II	47	239.4±5.4	23.7	11.0	<0.001

*Period I, Winter quarter, 1957. Period II, Spring quarter, 1958.

higher in countries where serum cholesterol levels are relatively high than in countries where cholesterol levels are low.[5] In this country, mean cholesterol values for patients suffering from coronary disease are higher than for the population in general.[6] Thus any factor that leads to the production of higher serum cholesterol levels would appear to be worth studying as a possible factor in atherogenesis.

The present study suggests that emotional stress may be one such factor producing an increased serum cholesterol level in some individuals. Since quarterly final examinations are the only examinations given at the institution where this study was carried out, the emotional tension among the students should be at a maximum at this time. During the middle of the school quarters tension should be relatively low. The changes noted during the 2 quarters show remarkable similarities to each other, as do the results of this experiment when compared with those recently reported in the literature.[1, 2]

The mechanism for the effects of mental tension on serum cholesterol levels is not immediately apparent. Friedman and co-workers[1, 7] reported that increases in cholesterol values during occupational stress could not be explained on the basis of dietary changes. Stress of various types is known to produce endocrine changes in experimental animals.[8] Since blood lipid levels are influenced considerably by hormonal changes of many types, an endocrine imbalance during stress must be considered as a possible cause of changes in serum cholesterol. The high incidence of diseases resulting from atherosclerosis among business executives and others under constant pressure has led many individuals to believe that a causal relation exists between stress and these diseases. Only recently has there been any acceptable evidence to support this concept. More extensive studies are needed to reveal the significance of these preliminary observations.

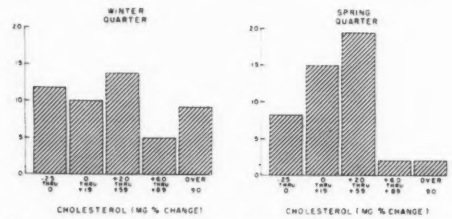

FIG. 1. Changes in serum cholesterols during comprehensive final examinations.

SUMMARY

The effects of quarterly final examinations on serum cholesterol levels in two large groups of freshman medical students were studied. During the 2 periods of examinations studied the mean cholesterol levels were elevated significantly over control periods of relative relaxation. The 2 groups of 50 and 47 male students showed a 16.5 per cent and 11 per cent increase in serum cholesterol levels during winter and spring quarter examinations, respectively.

SUMMARIO IN INTERLINGUA

Le effectos de final examines trimestral super le nivellos de cholesterol in le sero esseva studiate in duo grande gruppos de studentes medical in le prime anno de lor curso academic. Durante le 2 periodos de examines que esseva includite in le studio le nivellos medie de cholesterol esseva significativemente plus alte que durante periodos de controlo de re-

laxation relative. Le 2 gruppos consisteva de 50 e de 47 studentes mascule. Illes monstrava augmentos medie de 16,5 e 11 pro cento respectivemente in le nivellos de cholesterol seral durante le examines trimestral de hiberne e de primavera.

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Medical Eponyms

By Robert W. Buck, M.D.

Adie Syndrome. William John Adie (1886-1935), Physician, Charing Cross Hospital and Royal London Ophthalmic Hospital, etc., discussed "Pseudo-Argyll Robertson Pupils with Absent Tendon Reflexes, a Benign Disorder simulating Tabes Dorsalis" in *The British Medical Journal* 1: 928-930 (May 30) 1931.

"I wish to draw attention to a benign symptomless disorder characterized by pupils which react on accommodation but not to light, and by absent tendon reflexes.

"Five of the six cases I am about to describe came under my notice in the course of a few weeks; the condition therefore cannot be very rare. Though harmless in itself it merits recognition because it is often mistaken for a manifestation of syphilis of the nervous system, with unfortunate consequences for the patients and their families.

" . . . The true Argyll Robertson pupil reacts promptly and fully, often excessively, on convergence, and dilates again as soon as the effort to converge the visual axes is relaxed. In these cases the pupils show the so-called myotonic reaction; they do not respond to light; they contract very slowly through a wide range during a sustained effort to converge, often remain small long after the effort ends, and, when they dilate again, do so slowly. . . .

"It seems to me more than probable that some . . . cases with non-leutic Argyll Robertson pupils but normal tendon reflexes are examples of a milder form of the same benign disorder that I have described here."

The Aortic Arch Syndrome (Pulseless Disease)

A Report of Ten Cases With Three Autopsies

By W. M. THURLBECK, M.B., CH.B., AND J. H. CURRENS, M.D.

ROBERT ADAMS described a patient in 1827[1] whose arterial pulses were not palpable (fig. 1), and this is the first recorded case of "pulseless disease" that we have been able to find. The term in recent time has been used[2-9] to describe a peculiar syndrome in young women, usually Japanese, characterized by the absence of arterial pulsation in the arms and neck, often associated with cataracts and peculiar vascular abnormalities of the retinae. The optic changes were described by Takayasu[10] and the syndrome bears his name, although the absence of radial artery pulsations was mentioned only in the discussion of his report. Any disease of the aortic arch, however, can produce a similar picture of absent arterial pulsation in the arms and neck. Ross and McKusick[11] used the term "aortic arch syndromes" to describe these diseases and their effects. These authors found syphilitic aortitis to be the common cause of these syndromes in Baltimore and considered atherosclerosis alone to be a rare cause.

Experience at the Massachusetts General Hospital suggests that atherosclerosis with or without superimposed thrombosis is a more common cause of this syndrome than is generally realized. It is the purpose of this paper to describe 10 patients with pulseless disease and to discuss the etiology and the pathology with particular reference to 3 patients on whom autopsies were performed.

METHODS

Ten patients have been observed in the hospital between 1952 and 1957. All these cases had in common absent or diminished pulsations and blood pressure readings in one or both arms. In addition to the usual clinical and laboratory investigations the blood pressures were determined in 4 patients by a recording machine,[12] which picks up Korotkov vibrations over the brachial artery when these are indistinct or inaudible on auscultation. Autopsies were performed in the routine manner on the 3 patients who died in the hospital.

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RESULTS

The case histories of the 10 patients and the significant autopsy findings in 3 are presented below. Tables 1 and 2 summarize the clinical features of these cases.

Case 1. A 54-year-old man was admitted on March 9, 1954, because of attacks of fainting. In the 6 years prior to admission he suffered dyspnea and substernal choking on exertion, bilateral claudication, a myocardial infarction, transient episodes of blindness, dizzy spells, 2 episodes of unconsciousness, episodes of numbness and weakness of the right hand, failing memory, and aphasia. Past and family histories were noncontributory.

On physical examination feeble pulsations of the femoral and the dorsalis pedis arteries were the only pulses that were palpable. Blood pressure in the legs was 160 systolic. The fundi showed normal disks, multiple microaneurysms, many peripapillary fusiform vascular dilatations, and irregular venous dilatations with congestion and sluggish flow. The retinal artery pressure was 17/13 mm. Hg O.D. and 11 mm. Hg O.S. with insignificant pulse pressure. Speech was slow and hesitant, words were occasionally misused, and syllables were reversed.

Laboratory examinations of blood and urine were normal. An electrocardiogram showed Q waves in leads II, III, and aV_F with upright T waves. X-ray of the chest showed no calcification or dilatation of the aorta. Intravenous pyelogram was negative. The Hinton test for syphilis was negative.

Under hypothermia thrombendarterectomy of the innominate and left common carotid artery was performed (fig. 2). The innominate and left common carotid arteries were found occluded proximally, with no blood flow through the former and little through the latter. After thrombendarterectomy, flow was good through the left common carotid but the innominate artery thrombosed almost immediately. A bypass arterial shunt was

TABLE 1.—*Clinical Data*

Case no.	Age, sex	Duration of symptoms (yrs.)	Coronary heart disease with angina pectoris or myocardial failure	Claudication	Congestive heart failure	Stroke	Mental deterioration	Syncope	Transient blindness	Diabetes mellitus
1	54M	5	+	+	0	0	+	+	+	0
2	50M	10	+	+	+	0	+	0	0	0
3	54M	3	0	+	0	0	0	0	0	0
4	54F	0.5	0	0	+	+	+	0	0	0*
5	55M	8	+	+	0	0	0	0	+	0
6	70?1	12	0	0	+	0	0	0	0	+
7	81F	0	0	0	0	0	0	0	0	0
8	51F	10	+	0	+	0	0	0	0	0
9	50F	5	0	+	0	0	0	0	+	+
10	46F	3	0	0	+	+	+	+	0	0

*Three siblings had diabetes.

then placed between the ascending aorta and the right common carotid artery. The patient tolerated the procedure well, but during the warming phase postoperatively ventricular fibrillation occurred. Cardiac massage was instituted after 3 to 4 minutes, and the heart began to beat spontaneously after 3¼ hours of manual massage and electric defibrillation.

The patient regained full consciousness with a regular and good pulse, but then developed progressive respiratory difficulty from left ventricular failure and died of acute pulmonary edema 48 hours postoperatively.

At autopsy the ascending aorta and the arch of the aorta showed numerous, lipoid plaques involving 50 per cent of the surface of the arch and ascending portion; the intima was ulcerated over 1 plaque, 1.5 cm. in diameter, proximal to the innominate artery and adjacent to the site of the graft. The aortic valve and coronary ostia were normal and there was no dilatation or calcification of the aorta. The abdominal aorta was severely atherosclerotic with many large, ulcerated plaques covered with a thin plate of red-brown thrombus. In the descending thoracic aorta, iliac, and femoral arteries were numerous slightly raised, lipoid streaks.

The entire innominate artery was occluded by a red-brown, shiny, slightly adherent, granular thrombus. Its walls were focally calcified, and beneath the thrombus were streaks of fatty material. The right common carotid artery showed a single lipoid streak. The right internal carotid artery showed some calcification and a plaque that narrowed the lumen about 20 per cent. The homograft connecting the ascending aorta to the right common carotid artery was patent.

The left common carotid artery at the site of incision was patent. The left internal carotid artery in its proximal 2 cm. was obstructed by a fibrofatty thrombus through the center of which was a lumen 1 to 2 mm. in diameter; the wall of the vessel in this region was focally calcified. The proximal 3 cm. of the left subclavian artery was also occluded by a light brown fibrous thrombus with a central lumen 1 to 2 mm. in diameter; the wall in this region was atherosclerotic and calcified. The vertebral arteries were patent, soft, and about twice normal size. The visceral branches of the aorta had occasional atherosclerotic plaques but no significant obstruction.

Microscopic examination of multiple sections through the aorta and its branches showed severe atherosclerosis, but no syphilis or other arteritis. The occlusions of the left internal carotid and left subclavian arteries showed organized, canalized thrombi in severely atherosclerotic vessels, with many pigment-filled macrophages in the subclavian thrombus and a few in the internal carotid thrombus. The innominate artery was occluded by a recent antemortem thrombus.

The heart weighed 520 Gm. and showed signs of cardiac massage. There was severe diffuse sclerosis of the coronary arteries with almost complete, old occlusion of the anterior descending branch of the left coronary artery. The lumens of several other portions of the coronary arteries were reduced by half. Microscopically, the heart showed focal interstitial and perivascular fibrosis.

The brain weighed 1,350 Gm. The cerebral vessels were free of atherosclerosis. Gross and microscopic examination of the brain revealed multiple small areas of infarction, more on the

TABLE 2.—*Clinical Examination and Laboratory Data*

Case no.	Pulses				Blood pressure			Electrocardiogram	Blood sugar (mg.%)	Hinton test	Cholesterol (mg. %)	Other	Treatment	Course
	Radial R	Radial L	Carotid R	Carotid L	Femoral R	Femoral L	Arm	Leg	Machine (arm)					
1	0	0	0	0	+	+	0	150S	85/70	Myocardial infarction (post.)	85	Neg.	214		Endarterectomy and graft	Died
2	0	0	0	0	0	0	0			Nonspecific T wave & ST changes	85	Neg.	186	Cheyne-Stokes resp.		Died
3	+	0	+	+	+	+	150/90 (R)			Myocardial infarction (post.)	122	Neg.	240			Died
4	0	0	?	0	+	+	0	150/80 (L)		Myocardial infarction (post.)	2 hrs. pc 115	Neg.	408	Homonymous hemianopsia (R)		Leg amputation but living 3½ yrs. later
5	0	+	0	+	+	+	160/80 (L)		80 Syst. (R)	Myocardial infarction (post.)	—	Neg.	280		Diemnarol	Improved 1 yr. later
6	?	?	+	+	+	+	140/70 (intra-arterial)			—	231					Died 3 mos. later
7	0	0	+	+	+	+	0	130 Syst.		LVH	—		—			Died 3 yrs. later
8	0	0	+	+	+	+	0		150/120 (R)	LBBB	94	Neg.	327	Hypothyroidism		Died 4 weeks later
9	0	0	0	0	+	+	0	130/70 (R&L)	60/45	Nonspecific T-wave changes	90	Pos.	394		Diemnarol, penicillin, low-fat diet	Alive and better 2 yrs. later
10	+	sl.	thrill	0	0	sl.	140/90 (R) 80/60 (L)			LVH, ST and T wave changes	95	Neg.	280 to 354 mg.			Died 4 weeks later

LVH, left ventricular hypertrophy.
LBBB, left bundle-branch block.

ft than the right, located chiefly in the cortex supplied by the middle cerebral artery and the "watershed zone" between this artery and the anterior and posterior cerebral arteries. The area supplied exclusively by the posterior cerebral artery was spared.

The vessels of the retina showed innumerable fusiform aneurysms as well as fusiform dilated vessels that ought to be veins (fig. 3).

Case 2. A 50-year-old laborer, was admitted to the hospital in October 1953 complaining of severe shortness of breath for 1 month.

Over a 10-year period, the patient suffered bilateral intermittent claudication and coldness of the feet and an ulcer of the right leg for which bilateral lumbar sympathectomy and later a right midthigh amputation were performed. Thereafter angina pectoris developed, and cardiac enlarge-

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mained for six weeks, with little alteration in his symptoms, except that his strength was observed declining daily and his breathing becoming more difficult: his rest during the night was still more imperfect: during the entire of this distressing period, *no pulse was to be felt in any artery in the body:* although I daily made the most careful examination, it was in vain.

FIG. 1. From a case report by Mr. Robert Adams published in the Dublin Hospital Reports in 1827. It concerned a 68-year-old physician, whose pulses disappeared after an attack of chest pain, and who died 6 weeks later.

ment and absent peripheral arterial pulsations, except possibly for a weak right carotid pulsation, were observed.

The patient's father had died at age 50 and his mother at the age of 52, each of a "heart attack."

On physical examination Cheyne-Stokes breathing was striking, the blood pressure was unobtainable in either arm, and no distinct pulsations could be felt anywhere in the body except over the abdominal aorta. The optic disks appeared distinct in outline, and there was no arteriovenous nicking. The arterioles, however, were easily obliterated by slight pressure on the eye. His vision was good in each eye. The neck veins were not distended in the upright position and did not pulsate. The heart was enlarged 1 cm. to the left of the midclavicular line and no murmurs were heard. The liver extended 3 fingerbreadths below the costal margin in the epigastrium and was nontender. There was a right midthigh amputation. Responses to complex commands were delayed, but there was no definite motor or sensory abnormality, and the reflexes were normal except for absent abdominal reflexes.

Laboratory studies were not significantly abnormal except for the electrocardiogram, in which Q waves and ST and T changes suggested a previous posterior myocardial infarction. Blood Hinton tests for syphilis were negative on 2 occasions.

Severe Cheyne-Stokes breathing and dyspnea persisted without relief. On the third hospital day a venous circulation time with Decholin was 61 seconds with a fair endpoint. Approximately 10 minutes later, he developed severe respiratory distress with cyanosis, rapid breathing, tachycardia of 130, and circulatory collapse, and he died within 5 minutes. This episode was considered to be a fatal drug reaction to sodium dihydrocholate.[13]

Autopsy revealed severe extensive atherosclerosis of the aorta with much intimal ulceration involving the whole aorta (fig. 4). The aortic cusps and coronary ostia were normal and the ascending aorta was not dilated. The origins of the innominate, left common carotid, and left subclavian arteries were occluded by an adherent red-brown thrombus (fig. 5). The entire innominate artery showed severe atherosclerosis and calcification with occlusion extending to the origins of the right subclavian and common carotid, whose origins were narrowed to slits. Beyond this point the vessels were soft and patent. The left common carotid and left subclavian arteries were almost completely occluded in their proximal portions by calcified fibrofatty material (fig. 6). The left common carotid above the clavicle and the left subclavian and its distal branches were soft and patent. The distal abdominal aorta, common iliac, and left femoral arteries were completely occluded by rubbery, dark yellow clot. Microscopic examination of the aorta showed severe atherosclerosis but no evidence of syphilis or other arteritis. The innominate and left common carotid artery were markedly atherosclerotic and occluded by an old organized canalized thrombus.

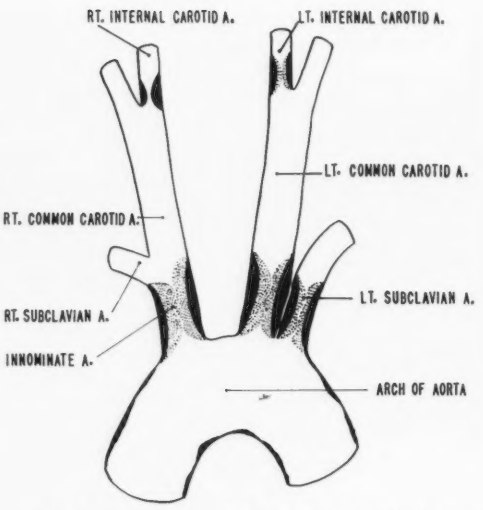


FIG. 2. The extent of atherosclerosis (*black*) and thrombosis (*stippled*) in case 1 at the time of operation.

The heart weighed 530 Gm. and extensive old infarcts were found in the interventricular septum and posterolateral left ventricle. Recent mural thrombi were present in the lateral wall and apex of the left ventricle and in the right atrial appendage. There was severe coronary atherosclerosis, the lumens being reduced to pinpoint size in many areas. Microscopically old infarction and extensive recent infarction (about 48 hours old) were

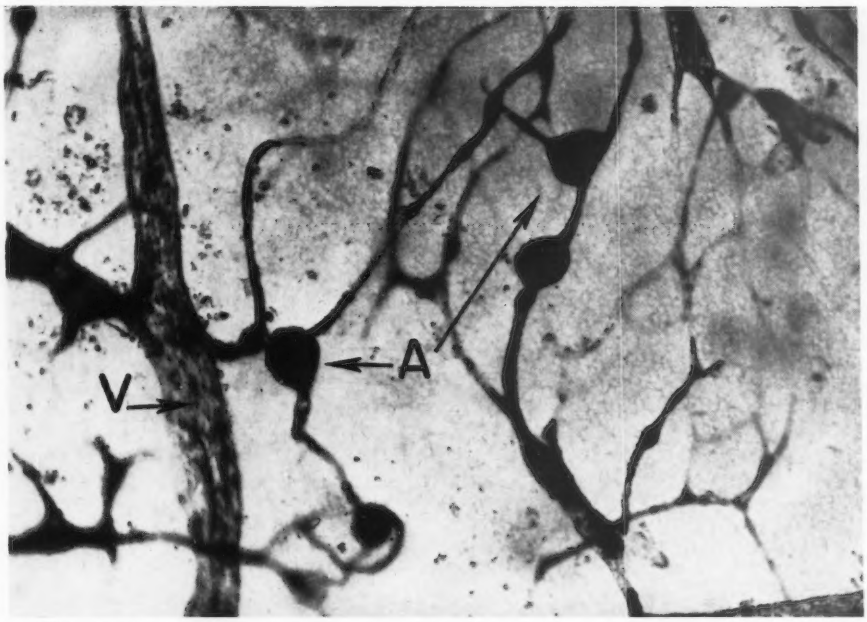


FIG. 3. The retinal vascular system was injected with dye to illustrate the small vessels with frequent microaneurysm (*A*) and fusiform dilated vessels (*V*), thought to be veins. (*Courtesy of Dr. Taylor Smith.*)

found in the lateral left ventricle and the right atrium.

The brain weighed 1,250 Gm. Multiple small friable and slightly discolored areas of infarction in the cortex and subcortical white matter on the superior medial region of both cerebral hemispheres were found that were of varying age and ranged in size from half a gyrus to minute microscopic areas. These lesions were distributed in the "watershed areas" of the anastomosis between the anterior cerebral arteries and the middle cerebral arteries and between the middle and posterior cerebral arteries, suggesting that they were due to diminished hydrostatic pressure. Many of the lesions consisted of reacting microglia rather than more severe infarction or cavitation, also suggesting a markedly diminished, but not completely deprived blood supply.

Case 3. A 54-year-old unmarried plumber, was admitted on July 4, 1956, with scrotal swelling for 1 week. Three years earlier he developed intermittent claudication and femoral arteriograms showed obliteration of both profunda femoris arteries and the left superficial femoral artery. A homologous femoral arterial homograft gave temporary improvement but it thrombosed after 11 months and a left midthigh amputation was necessary later.

On physical examination the blood pressure was 150/90 in the right arm, and no pulse or blood pressure could be obtained in the left arm. Both carotids, the right radial, both femoral, and the right dorsalis pedis arteries were normal. The right popliteal and posterior tibial pulsations could not be felt. The right scrotum was swollen, red, warm, and tender.

The urine showed albumin. No white cells or bacteria were seen in the urinary sediment. The hemoglobin was 11.2 Gm. per cent, and the white blood count was 20,500 with 80 per cent neutrophils. Acidosis and azotemia were present and an electrocardiogram suggested an old posterior myocardial infarct. X-ray of the chest showed cardiomegaly with no abnormality of the aorta. Blood Hinton tests for syphilis were negative on 4 occasions.

On the ninth hospital day a right orchidectomy was performed and acute orchitis and epididymitis with abscess due to *Bacillus coli* were found. The patient became progressively uremic following surgery and died on the eighteenth hospital day.

Autopsy showed severe atherosclerosis involving the entire aorta. Large ulcerated atherosclerotic plaques, with mushy red-brown grumous material at their bases, involved about one fifth of the aorta and were most marked in the distal thoracic

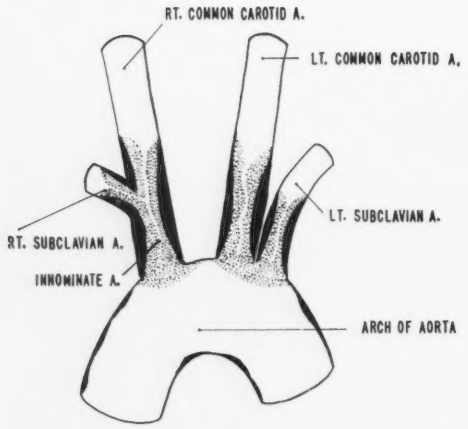


FIG. 4. The extent of atherosclerosis (*black*) and thrombosis (*stippled*) in case 2.

and abdominal aorta. Between the ulcerated plaques were many thickened, yellow, lipoid streaks. The aortic valve and coronary ostia were normal, and the ascending aorta and arch were not dilated. The origin of the left common carotid artery was narrowed to a slit and the left subclavian artery was occluded near its origin by atherosclerotic plaques (fig. 7). The innominate artery was relatively free of atherosclerosis. The left external iliac artery was occluded by a fibrofatty thrombus and the remaining iliac vessels showed severe atherosclerosis.

Microscopic examination showed severe atherosclerosis, with no evidence of syphilis or other arteritis. The left subclavian and left common carotid arteries were almost occluded by severe atherosclerosis with superimposed, organized and canalized thrombus.

The heart weighed 600 Gm., with a thick left ventricle. An area of old fibrosis involved the posterior left ventricle and septum and there was questionable mild old rheumatic mitral valvulitis. The coronary arteries showed diffuse atherosclerosis with an old occlusion of the right coronary artery midway in its course.

The kidneys weighed 85 Gm. each and showed old pyelonephritis, nephrosclerosis, and healing lower nephron nephrosis.

The brain weighed 1,300 Gm. and the cerebral vessels showed minimal atherosclerosis. Microscopic examination showed multiple small areas of cortical infarction.

Case 4. A 54-year-old woman was admitted on December 5, 1952, because of aphasia.

Seven months earlier no blood pressure was obtainable in either arm. Three months prior to admission she developed pain in the right eye, poor vision, unsteadiness, slight aphasia, and thick speech.

Three siblings had diabetes mellitus. For many years she had an excessive alcohol intake but stopped 3 years previously.

On physical examination the blood pressure was 150/80 in the left leg. Both radial and brachial arteries, the left carotid artery, and both posterior tibial arteries could not be palpated. Pulsations of the right carotid artery were felt by some observers but not by others and both femoral arteries and dorsalis pedis arteries pulsated. Coarse rales were heard at both bases. The left pupil was slightly larger than the right and was irregular and there was a right homonymous hemianopsia and a sustained nystagmus on lateral gaze. Hearing was decreased in the right ear. Coordination was slow on the right. She was disoriented as to place and time. She could follow simple commands but not complex ones. Speech was slurred and she had anomial aphasia of which she was aware.

Abnormal laboratory findings included a white cell count of 17,000 and a serum cholesterol of 405 mg. per cent. On x-ray the heart, aorta, the neck and skull were normal. Lumbar puncture was negative but a pneumoencephalogram showed ventricular dilatation due to cortical atrophy. An electrocardiogram showed an old posterior myocardial infarct. Hinton tests of blood and cerebrospinal fluid were negative.

The patient's condition changed little during her hospital stay and for the subsequent 3½ years except for a leg amputation.

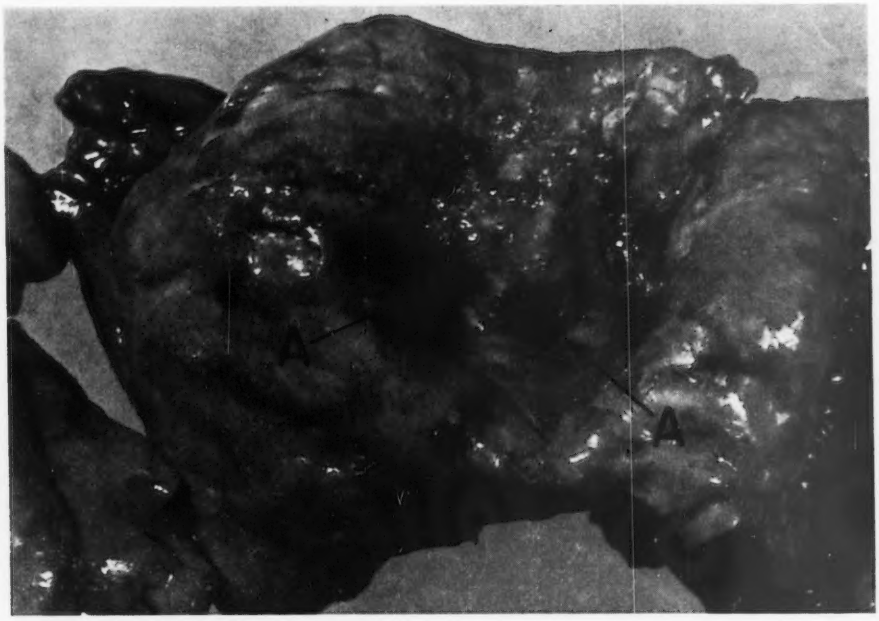
Case 5. A 55-year-old male clerk suffered over an 8-year period cardiac pain, intermittent claudication, recurrent episodes of visual loss and pain in the right eye, and finally episodes of tingling of the left thumb and weakness of the left arm.

The blood pressure was 160/80 in the left arm and 80 systolic in the right arm by machine.[12] No pulsation was felt in the right arm or right neck or below the femoral arteries. Blood pressure in the right arm by the indirect machine method[12] was 80 mm. systolic. The left carotid and radial arteries pulsated normally.

Examination of the urine and blood was normal, the serum cholesterol was 280 mg. per cent, an electrocardiogram showed an old myocardial infarct, and the blood Hinton test for syphilis was negative.

After a long period of anticoagulant therapy there was good subjective improvement, and weak pulsations were palpable in the right radial and carotid arteries.

Case 6. A 70-year-old man with diabetes mellitus for 12 years and congestive failure for 3 weeks had no blood pressure in either arm. Faint pulsations were felt in both radial arteries, but there were no pulsations of the dorsalis pedis and posterior tibial arteries. A grade-II systolic murmur was heard at the apex. There was mild pitting



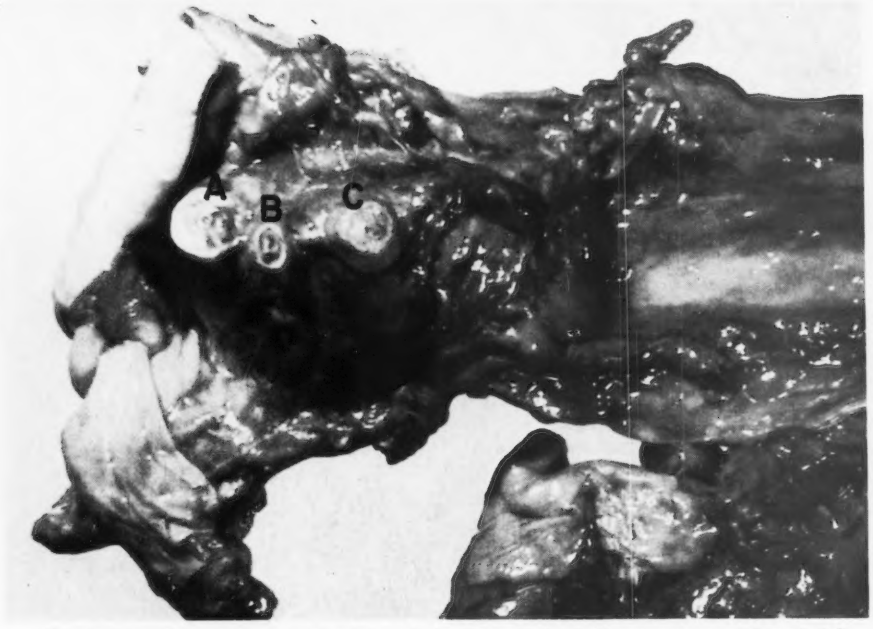


FIG. 5 *Top.* Case 2. Region of origin of the innominate, left common carotid, and left subclavian arteries viewed from the inside of the aorta. Note the dark areas that represent recent red and brown thrombus formation (*A*).

FIG. 6 *Bottom.* Case 2. The innominate (*A*), left common carotid (*B*) and subclavian (*C*) arteries cut in cross section close to their origin from the aorta. Note the severe atherosclerosis and thrombosis that occludes or nearly occludes the arteries.

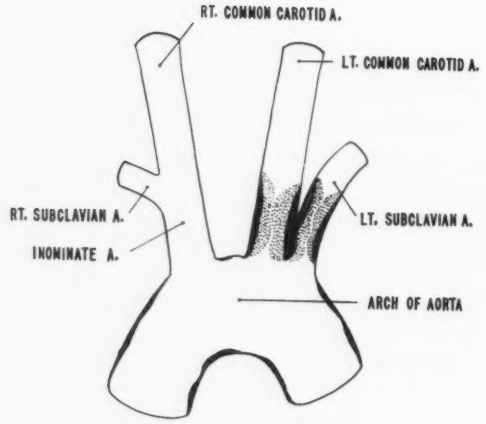


FIG. 7. Extent of atherosclerosis (*black*) and thrombosis (*stippled*) in case 3.

edema of both ankles and free fluid in the abdomen.

The urine was normal. The fasting blood sugar was 231 mg. per cent. Two blood Hinton tests for syphilis were negative. On intra-arterial puncture the blood pressure was found to be 140/70 in the right arm.

The patient died 3 months later at another hospital. Autopsy revealed severe generalized atherosclerosis. The "vessels to the neck" were "tortuous and calcified but patent." There were severe coronary atherosclerosis and extensive myocardial fibrosis. There was no evidence of syphilis.

Case 7. An 81-year-old woman had absent blood pressure in both arms for 4 years. On physical examination the blood pressure was 130 systolic in the right leg. No pulsations or blood pressure could be found in the arms. There were bilateral subclavian, carotid, femoral, and popliteal pulsations. Physical examination was otherwise unremarkable.

The urine and blood were normal. X-rays of the chest showed cardiomegaly and a tortuous and calcified aorta. X-ray of the ankle showed an old trimalleolar fracture of the right ankle and Paget's disease of the left os calcis with calcification of the arteries in this region. An electrocardiogram suggested left ventricular hypertrophy and a blood Hinton test for syphilis was not recorded.

The patient died at home 3 years later, allegedly of a "stroke." No autopsy was performed.

Case 8. A 51-year-old woman had an episode of chest pain lasting a few minutes 10 years before admission. At that time chest x-ray showed cardiomegaly and her blood pressure was said to be more than 200 systolic. One year prior to admission she noticed increasing dyspnea on exertion and a gain in weight, relieved temporarily by mercurial injections.

Four to six months prior to admission she developed anorexia and loss of weight. Four weeks before admission she was given digitalis.

Her parents died in their middle 70's of coronary thrombosis as did a brother at age 54. Two siblings were alive and well.

Pulsations were not obtainable in either arm or in the region of the subclavian, axillary, brachial, or radial arteries. Both carotid arteries had forceful pulsations. Both femoral arteries had poor pulsations and pulsations were absent below them.

The heart was enlarged 3.5 cm. to the left of the midclavicular line and the apex beat was heaving. Dullness and rales were heard at both lung bases, and there was pitting edema of the legs.

Examination of the urine and blood was negative. The nonprotein nitrogen varied from 80 to 114 mg., the cholesterol was 327 mg., and the protein-bound iodine was 1.3 gamma per 100 ml. The radioactive iodine uptake was 22 per cent. The basal metabolic rate was —16.

Chest x-ray and fluoroscopy revealed a greatly enlarged heart with poor pulsations. The aorta was negative. An electrocardiogram showed left bundle-branch block. The blood Hinton test for syphilis was negative on 2 occasions. The blood pressure by the machine method[12] was 150/120 in the right arm. A clinical diagnosis of myxedema was not made although the laboratory data suggested hypothyroidism.

The patient was treated for cardiac failure, but she died after a month; an autopsy was not performed.

Case 9. A 50-year-old woman noted for 1 year muscular weakness and fatigue, particularly in the arms, usually after walking 1 block. Approximately 6 months later she noted transient episodes of complete blindness of the left eye recurring several times daily, unrelated episodes of paresthesia of the hands, nose, and mouth, and aching substernal chest pain, coming on once or twice a week.

The hands and feet were warm and red on examination while the face appeared somewhat cool and clammy. No carotid, brachial, or radial pulses were felt. The femoral pulses were palpable. The blood pressure in both legs was 130/70. No blood pressure could be obtained in either arm by the usual methods. The arm blood pressure by an indirect machine method[12] was 60/45 (fig. 8). A continuous bruit and thrill were noted over the right carotid above the clavicle.

The urine and blood were normal. The serum cholesterol was 394 mg. per cent. Glucose tolerance tests showed a diabetic curve. X-ray of the chest showed a slightly elongated aorta. An

electrocardiogram demonstrated nonspecific T-wave changes. The blood Hinton test for syphilis and the treponema pallidum immobilization test were positive. The cerebrospinal fluid Hinton test for syphilis was negative.

The patient was treated with penicillin, a strict low-fat diet, and Dicumarol. Two years later, angina pectoris intermittent claudication, and visual disturbances were less prominent than before. Examination at this time showed faint pulsation in the right radial artery and a blood pressure in the right arm of 90/70.

Case 10. A 46-year-old woman 3 years prior to admission gradually developed mood and personality changes, with depression, confusion, poor memory, and weakness and stiffness of the right arm. About 18 months prior to admission after an attempt at suicide she was found to be confused and dysarthric with mood lability. At this time she had a right homonymous hemianopsia and a right spastic monoplegia. Cerebrospinal fluid pressure, skull x-rays, pneumoencephalogram, and electroencephalogram were normal. A few weeks later an episode of cardiac syncope occurred following which atrial fibrillation and poor pulses in the left arm were noted.

Five days before admission she had an episode of confusion accompanied by headache. Immediately before admission she had cardiac syncope again.

Her father died of "angina" and the mother died of a stroke, both at an unknown age. One sister was alive and well.

On physical examination the pulse was 92 and regular, the blood pressure was 140/90 in the right arm, 80/60 in the left. The left common carotid artery did not pulsate. There was a thrill over the right common carotid. The left radial and femoral arteries pulsated poorly and the right femoral artery could not be felt. Crackling rales were heard at both lung bases. There was a moderate systolic murmur at the base of the heart. A systolic bruit was present over the entire abdomen.

The patient was confused and disoriented. Her memory was poor. She named objects and did simple calculations poorly. There was a hypermature cataract in the left eye. The right eye showed some arteriovenous nicking and tortuosity of the vessels. The right arm was weak and spastic. The right plantar response was extensor.

Laboratory examinations revealed albuminuria, elevated white cell count on admission of 23,000 per mm.,^{3} and a serum cholesterol of 354 mg. per cent. A blood Hinton test for syphilis was negative.

X-rays of the chest on admission showed pulmonary edema, which cleared 10 days later. The heart was borderline in size and the aorta was negative. Marked calcification of the abdominal aorta was seen. The left kidney did not fill on intravenous pyelography. An electrocardiogram showed left ventricular hypertrophy and widespread S-T depression and T-wave inversion.

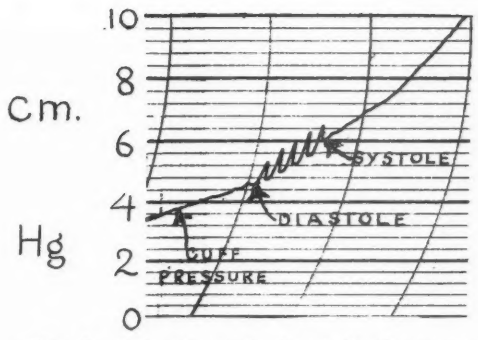


FIG. 8. A tracing made by a blood pressure machine[12] on patient 9. The appearance and disappearance of the Korotkov vibrations are superimposed on the pressure curve from the pneumatic cuff. The tracing is read from right to left and the blood pressure is 6/4.5 cm. Hg.

The patient complained of intermittent abdominal pain and later suffered marked dyspnea and left pleuritic chest pain. Pulmonary congestion and left pleural effusion were found. Her cardiac failure improved somewhat but she died at home 4 weeks later and an autopsy was not performed.

DISCUSSION

While atherosclerosis and thrombosis of the internal carotid is fairly common,[14-16] atherosclerosis of the arch of the aorta with occlusion of the great vessels is rare as judged by reports in the medical literature. Occasional cases of atherosclerotic occlusion of the common carotid artery extending to the aorta have been recorded[17, 18] as have cases with diminution or absence of pulsation in either arm, thought to be due to atherosclerosis.[11, 19] Clinical cases with involvement of 2 or more of the great vessels by atherosclerosis are even more rare; only 8 cases being described.[11, 20-23] We agree with Ross and McKusick that Bittorf's[24] case is not clearly due to atherosclerosis. The only autopsied case of occlusion of the great vessels due solely to atherosclerotic occlusion that will stand critical analysis is that of Abrams and Gore[25] but even in this case underlying syphilitic aortitis cannot be completely excluded on the basis of the data presented. Broadbent's[26] patient "had at one

time been a sailor, had lived intemperately and had syphilis," and at autopsy had a dilated ascending aorta; no microscopic examination was made. Two other cases sometimes accepted as being atherosclerotic in origin[27, 28] should be rejected as such, since in one case[27] there was an extensive panarteritis and medial degeneration and in the other[28] extensive elastic degeneration and fragmentation. Dissecting aneurysm of the aorta may have been the disease in Adam's[1] case, but there was no description of the aortic arch or vessels.

We have no doubt that atherosclerosis and thrombosis was the cause of the disease in our 3 autopsied cases. These patients had severe diffuse atherosclerosis, intermittent claudication, and coronary heart disease. Despite intensive search there was no evidence of aortitis. Although thrombus was present in the left ventricle in case 2, and this might suggest an embolic origin of the occlusions, the histologic appearance of the occlusions of the great vessels indicated that they had preceded the thrombi in the heart.

We can only guess at the etiology of the remaining cases. Case 9 was the only instance with positive serologic tests for syphilis and may represent syphilitic aortitis. The remaining cases illustrate the difficulty of diagnosis without the benefit of an autopsy. There is evidence of generalized atherosclerosis, or factors predisposing to atherosclerosis, in most of them and we consider that they may be due to atherosclerosis, but syphilitic aortitis or other more obscure forms of aortitis cannot be excluded without complete autopsy. Case 8 had laboratory evidence of myxedema, which may have been responsible for her large, poorly pulsatile heart and could have predisposed to atherosclerosis.

The family histories of these 10 patients as obtained from the hospital records are of interest and indicate a high incidence of coronary heart disease. Of the total of 20 parents 6 died of coronary heart disease and 2 more were thought to have died of coronary disease. None of the parents was listed as having diabetes and only 1 was said to have an elevated blood pressure. There were 33 siblings and 4 of the siblings were known to have coronary disease and 4 more thought to have coronary disease. Four siblings were known to have diabetes and 2 were said to have an elevated blood pressure.

It is thought that the disease is the same in the 3 autopsied cases as occurs in people with atherosclerosis although the element of thrombosis was prominent. The only unusual feature in these patients seemed to be the location of the atherosclerosis and thrombosis to involve the arch of the aorta particularly at the ostea of the large vessels. The gross association of thrombosis and atherosclerosis in these autopsies can be used to support Duguid's concept that thrombosis "instead of being an occasional complication of atherosclerosis, is an important factor in its pathogenesis."[29] Estimation of fibrinolytic activity of the blood was not done.

The sex incidence in the 10 cases reported here is equal, indicating that the disease does not have a predilection for either sex. This is in distinct contrast to the variety that seems to affect the younger people in Japan and that is predominantly a disease affecting females (111 females and 11 males),[5] suggesting an inherited sex-linked factor.

The nomenclature of this group of diseases of the aortic arch remains a problem. The symptoms are similar because they affect the same anatomic region. The syndromes so produced may vary slightly because of the underlying disease process. For example, the aortic arch syndrome as it occurs in Japan would also include the facts that the patients are usually young, female, have a strongly positive tuberculin test, and an elevated erythrocyte sedimentation rate. The best term for the whole group would appear to be "the aortic arch syndrome" and we would describe our cases as "the aortic arch syndrome, due to atherosclerosis and thrombosis" (cases 1, 2, and 3), "probably due to syphilis and atherosclerosis" (case 9), and "of unknown etiology, possibly atherosclerosis" (remaining cases). Many other names have been used to describe this whole group. Of these "chronic subclavian-carotid syndrome"[21] is one of the best, but perhaps the innominate artery should not be excluded as it is by this

term. "Reversed coaretation,"[30-32] although a striking term, has already been criticized. "Pulseless disease" is manifestly a poor name, since there are only a few cases in which pulses cannot be felt clinically, and pulses in the legs are often easily palpable. Furthermore, we believe that even in the cases where pulses were not clinically palpable, pulses would be detected by the machine mentioned above. The disease is "pulse-poor" rather than "pulseless." The eponymous use of Takayasu[10] or Martorell[22] to describe this group of diseases has little to recommend it since Adams[1] described the first case.

A second problem is the term used to describe the aortic arch syndrome caused by arteritis in young females. The most commonly used term is "Japanese pulseless disease," but since this disease is neither Japanese nor pulseless, it seems a poor name.

Our attention was drawn to the striking symptom of intermittent blindness (amaurosis fugax) in cases 1, 5, and 9. In case 1 this was related to exertion and in case 5 it was on the side of the completely occluded carotid artery. Case 9 was observed in an attack and stasis of the retinal arteries and veins was seen then. This symptom would thus appear to be due to transient ischemia of the eye and due to the diminished blood flow in the ophthalmic artery. The changes in the eyegrounds of case 1 were thought to be similar to those described in "Japanese pulseless disease," and they may represent changes due to diminished retinal blood pressure. The eye findings of this patient and the changes found at autopsy and their significance are to be described in detail later.[33]

Treatment

Various forms of treatment have been used in the aortic arch syndromes including surgery,[20, 22] antispasmodics,[34] corticosteroids,[35] anticoagulants,[23] and a combination of the last two.[9, 36] Fairly good results have been claimed for anticoagulants,[23] with which we would agree. The progress of the disease was halted in 2 of our cases that have been kept on long-term anticoagulant therapy; these patients perhaps even improved slightly, with pulsation appearing in previously clinically nonpulsatile vessels. Case 9 also was treated for syphilis, however, and was given a low fat diet; while she was definitely improved, it is not possible to decide which method of treatment was responsible. The dietary restriction of fat with weight reduction may also be of help in patients with hypercholesteremia.

Summary

Ten patients are presented in whom absent arterial pulsations were noted in 1 or both arms. Six patients also had absent carotid arterial pulsations on 1 or both sides.

The blood pressure was determined satisfactorily by a machine devised to record the Korotkov vibrations. This indicates feeble arterial pulsation in spite of inability to palpate them clinically.

Three autopsied cases showed severe atherosclerosis with superimposed thrombosis.

Long-term anticoagulation used in 2 patients for as long as 3 years seemed to result in some clinical improvement.

Summario in Interlingua

Es presentate 10 patientes in qui le absentia de pulsation arterial esseva notate in 1 o ambe bracios. Sex del patientes habeva etiam absentia de pulsation del arteria carotidic a 1 o ambe lateres.

Le tension de sanguine esseva determinate satisfactorimente per medio de un machina construite pro registrar le vibrationes de Korotkov. Iste methodo reflecte debile pulsationes arterial in despecto del facto que illos non es clinicamente palpabile.

Tres necropsias monstrava sever atherosclerosis con superimposition de thrombosis.

Medication anticoagulatori, usate in 2 del patientes durante periodos de usque a 3 annos, pareva resultar in un certe melioration clinic.

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Blood Pressure and Obesity

By H. M. Whyte, D.Phil.

Previous surveys have shown that height of observed blood pressure and degree of overweight are related. However, excess weight does not necessarily mean excess fat and the possibility of error in the measurement of blood pressure due to variations in the size of the arm has not been excluded. The present survey, taking these factors into account, shows that blood pressure is influenced by the total bulk of the body but not especially by fat except insofar as it contributes to total bulk. A possible explanation of the findings is offered.

IT IS WIDELY accepted that hypertension is more common among the obese than among the lean and that a positive relationship exists between the level of blood pressure and the degree of obesity. The evidence upon which these common beliefs are based comes largely from numerous surveys that are fully discussed in standard books on blood pressure.[1, 2] However, there are several reasons why the conclusion that obesity and hypertension are related should not be accepted too readily.

Age has an important influence on blood pressure and care must be taken in analyzing observations to avoid confusion due to differences in age, even within relatively narrow age groups. Height and weight are obviously related and in seeking the true relationship between blood pressure and weight, or bulk, of the body, proper heed must be paid to variation in height among individuals. This is not easy and the problem is not satisfactorily overcome by referring to tables of standard weights or by using the ponderal index of bulk, weight per unit of height.[3] Then there is the difficulty relating to the circumference of the arm. It is well established[4] that our ordinary method of measuring blood pressure gives readings that are falsely high when the arm is big. Since big people generally have big arms, this error will exaggerate any true association that might exist between obesity and blood pressure. In analyzing the results of a survey among more than 17,000 individuals, Bøe and co-workers[5] drew the conclusion that age has a very marked influence on blood pressure, whereas the influence of weight, relative to age and height is very small. Indeed, when corrections were made for the probable errors attributable to size of arm, in the small number of subjects in which arm circumference was measured, it seemed that weight, or obesity, had no significant effect on blood pressure.

Thus, 3 factors likely to obscure the true relation between obesity and blood pressure are age, height, and size of arm. No previous surveys, to my knowledge, have taken into account all 3 of these factors, nor a fourth very important factor, obesity itself. It has always been assumed that excess weight is a measure of excess fat.

We have been interested in reexamining the question of obesity and blood pressure, among the natives of New Guinea[6] as well as in Australian men,[3] taking into account these various factors. Skinfold thicknesses have been accepted as a measure of obesity.[7] Neither the amount of fat nor the total bulk of the body had any demonstrable influence on blood pressure in the natives. In Australians, on the other hand, blood pressure was related to over-all bulk but not apparently to obesity per se. This latter conclusion was somewhat indefinite because of the influence of a wide age scatter and an unsatisfactory site for skinfold measurements. These drawbacks have been avoided in the survey which forms the subject of the present report.

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TABLE 1.—*Correlation Coefficients*

	Systolic B.P.	Diastolic B.P.	Age	Height	Weight	Arm circumference	Fat
Diastolic B.P.	+.583*						
Age	+.049†	+.019†					
Height	—.005†	—.038†	+.127†				
Weight	+.419*	+.373*	+.150†	+.481*			
Arm circumference	+.417*	+.399*	+.139†	+.156†	+.733*		
Fat	+.347*	+.306*	+.094†	+.003†	+.698*	+.573*	
Serum cholesterol	—.028†	+.040†	+.290‡	+.203§	+.233§	+.105†	+.071†

*To 0.1 per cent level of probability.

†Not significant of probability.

‡To 1 per cent level of probability.

§To 5 per cent level of probability.

METHODS

Observations were made on 100 apparently healthy men, 20 to 40 years of age. Height, without shoes, to the nearest inch was recorded, and weight, allowing for clothes, was recorded to the nearest pound. Circumference of the right upper arm was measured in centimeters. Subcutaneous fat was measured as the width, to the nearest millimeter, of the double fold of skin and subcutaneous fat that could be pinched up at each of 3 sites: para-umbilical, over the triceps, and over the inferior angle of the scapula. Measurements are valid only for the purpose of making comparisons, since the spring calipers which were used had spherical contacts and their closing pressure varied with thickness. The sum of measurements made in the 3 sites was used as an index of fatness.

Blood pressure was measured in the sitting position from the right arm with an aneroid type of machine, which was frequently checked against a mercury manometer. The cuff was 13 cm. wide and of the type fitted with metal braces and a clip. Pressure was recorded to the nearest even number of millimeters, the diastolic being taken at the point of disappearance of sound. Blood pressures were by no means basal, as most of the subjects were prospective donors of blood. It has been assumed that the obese and the lean did not differ in their reaction to the circumstances of the examination.

A sample of blood was taken at the conclusion of each subject's donation of blood, and serum cholesterol was measured by the method of Abel and colleagues.[8] The serum cholesterol level was also measured before blood donation in 10 subjects and found to be 2.8 per cent higher than the post-donation level.

RESULTS

Average values found in this series, together with standard deviations, were as follows: age 27.5 ± 4.9 years, height 69.0 ± 2.7 inches, weight 159.8 ± 22.6 pounds, circumference of arm 28.3 ± 2.5 cm., fat measurement 38.0 ± 14.6 mm., systolic blood pressure 132.5 ± 15.3 mm. Hg, and diastolic pressure 80.6 ± 11.2 mm. Hg. The total fat measurement was made up of abdominal fat 15.7 mm., arm fat 10.1 mm., and fat over the scapula 12.2 cm. The average weight relative to age and height was 107 per cent of the standard drawn from the tables of the Metropolitan Life Insurance Company: 95 per cent of observations fell between the limits of 80 and 134 per cent.

The coefficient of correlation for each pair of attributes is shown in table 1. The true significance of these coefficients is obscured by the fact that they take account of only 2 attributes while ignoring all others: the coefficient is made up of contributions from correlations involving the hidden attributes as well as the true correlation between the nominated attributes. For this reason partial correlation coefficients and regression equations were calculated to test the truth of the principal relationships in question.

Blood Pressure and Body Weight

The simple correlation coefficients indicate a strong correlation between blood pressure and body weight, as illustrated in figure 1. However, as weight is also related to height, fatness, and circumference of the arm, a positive relationship between blood pressure and

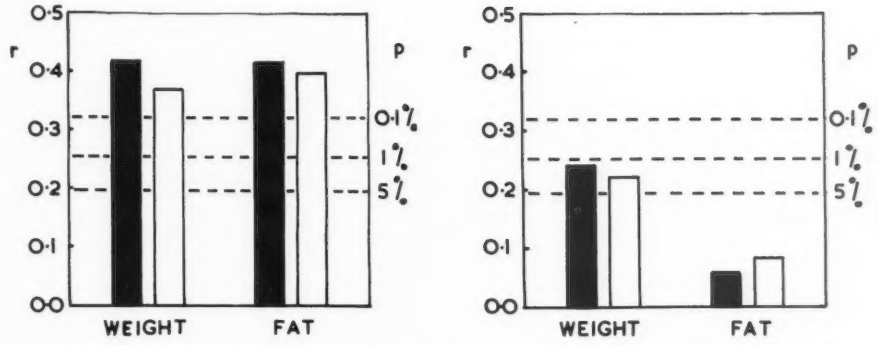

FIG. 1 *Left.* The simple coefficients of correlation between blood pressure and body weight, and blood pressure and body fat together with appropriate levels of probability. The *solid columns* refer to the systolic and the *open columns* to the diastolic pressure.

FIG. 2 *Right.* The coefficients of partial correlation between blood pressure and body weight when age, height, fatness, and size of arm are held constant; and between blood pressure and fatness (a negative coefficient) when age, height, weight, and size of arm are constant.

any of these other features could be causing an erroneous impression of the influence of weight on blood pressure. Age appeared to exert no influence. When allowance was made for the possible influences of age, height, fatness, and size of arm, there still remained a significant relationship between blood pressure and body weight that was significant at a 5 per cent level of probability (partial correlation coefficients were 0.243 for systolic and 0.223 for diastolic pressure). This is illustrated in figure 2 and means that blood pressure would be expected to increase with body weight in a population of men who were of uniform age and height and had the same size of arm and thickness of subcutaneous fat. The reduction in size of the coefficient when these other factors were taken into account was due mostly to the influence of size of arm, partly to height, and not at all to age and fatness.

Another indication of the relative importance of the influence of each of these factors on blood pressure comes from the regression equations. When each of the variables is expressed in its "normalized" form, that is, as deviation from its mean divided by the standard deviation, the regression coefficients are closely analogous to partial correlation coefficients and prove a measure of the relative importance of each item. The best fitting linear relationships expressed in these terms were found to be as follows:

Systolic pressure = +0.513 (weight) — 0.004 (age) — 0.272 (height) — 0.086 (fat) + 0.133 (arm size) (r = +0.241)

Diastolic pressure = +0.482 (weight) — 0.028 (age) — 0.292 (height) — 0.122 (fat) + 0.165 (arm —size) (r = +0.220)

With the other variables being held constant, it is obvious that weight exerts the greatest influence on blood pressure. The negative influence of height is an indication that it is not the absolute body weight, but rather weight relative to height that is the important factor. When the data were analyzed in other ways, it was found that the best index of body bulk relative to height was given by the ratio,[2] body weight/height. The partial correlation coefficients and regression coefficients derived by using this index were just as significant as when weight and height were included separately.

Expressed in ordinary units, the regression equations became:

Systolic pressure (mm. Hg) = 165 + 0.35 weight (lb.) — 0.01 age (yr.) — 1.55 height (in.) — 0.09 fat (mm.) + 0.81 arm size (cm.)

Diastolic pressure (mm. Hg) = 111 + 0.24 weight (lb.) — 0.06 age (yr.) — 1.22 height (in.) — 0.09 fat (mm.) + 0.73 arm size (cm.)

Blood Pressure and Circumference of the Arm

Although the simple correlation coefficients implied that blood pressure measured in the ordinary way was higher in subjects with larger arms—as would be expected in view of the observations made by Ragan and Bordley[4]—the association lost significance when the possible influence of other factors was excluded. With constant age, weight, height, and fatness, the partial correlation coefficients for the relations between arm circumference and systolic pressure (+0.097) and between the arm circumference and diastolic pressure (+0.120) were not significant. It must be concluded that arm circumference and blood pressure, as measured in this group of men, were unrelated. An important factor here might be the type of cuff which was used—one with metal braces and clip and not the commoner sleeve type. If the magnitude of any discrepancy between true intra-arterial pressure and observed pressure was directly related to the circumference of the arm the results would imply that the true pressure varied inversely with the size of the arm. This seems unlikely.

The circumference of the arm of men in this study could be predicted reasonably well from the height and weight: arm circumference (cm.) = 179.4 − 2.4 height (in.) + 0.1 weight (lb.) (r = +0.587).

Blood Pressure and Body Fat

Here, too, the simple correlation coefficients indicated a highly significant positive relationship (table 1 and fig. 1). However, when age, height, weight, and size of arm were held constant, the partial correlation coefficients became insignificant (−0.060 for the systolic and −0.084 for the diastolic pressure), as illustrated in figure 2.

The insignificant influence of fatness on blood pressure, all other variables being held constant, is also evident from the regression equations mentioned previously.

Serum Cholesterol

The average level of serum cholesterol in this series and the standard deviation were 214.7 ± 42.7 mg. per 100 ml. The cholesterol concentration appeared to be related to age, height, and weight. By the technic of partial correlation the association[2] with height (+0.091), weight (+0.135), and weight/height (+0.129) became unimportant but a significant relationship (to 1 per cent level of probability) with age remained (+0.264). There was no evidence that the cholesterol level was related to the thickness of subcutaneous fat or the blood pressure.

Discussion

Two conclusions to be drawn from the observations made in this study are quite clear-cut. The first is that the bigger and heavier a man is, in relation to his height, the higher will be his blood pressure. This is the same as most surveys have concluded. The second conclusion is that the composition of the excess weight is immaterial: it is the over-all bulk that counts, be it muscle or fat. Commonly, of course, it is fat.

To what extent is blood pressure affected by changes in weight? Assuming that the results of this survey can be applied to any one individual whose weight is changing, then the systolic pressure would be expected to rise by 10 mm. Hg and the diastolic by 7 mm. Hg for each increment of 28 pounds in body weight. This assumes there have been no concomitant changes in age, height, or arm circumference. If we take into consideration the average increase in size of arm to be expected with this gain in weight, then the rise in observed systolic and diastolic pressures would be of 12 and 9 mm. Hg respectively. The influence of weight on blood pressure in this group of men is 3 times greater than what has been reported among Norwegians.[5] It is in sharp contrast with the complete lack of relationship between blood pressure and body bulk in natives of New Guinea.[6]

Why should blood pressure increase with body weight? The following argument leads to a rather fanciful, though perhaps plausible, explanation. When weight increases, the bulk of tissue increases and there is an increase in the expenditure of energy and the demand

for blood. The vascular bed and the cardiac output must increase: cardiac output seems to be related to surface area, which, of course, increases with bulk. But what happens to blood pressure when the augmented cardiac output is forced into an aorta and elastic arterial reservoir that may not have increased in capacity as the body weight rose?

Let us assume that the size of the aorta does not increase. Then, taking average figures for pulse rate and cardiac output[9] we can calculate the expected increase in cardiac stroke volume for any particular increase in body size. In addition, from the volume-pressure characteristics of the human aorta,[10] we can predict the rise in pressure that this extra stroke volume will produce. Thus, for a man who is 30 years of age and 70 inches high the mean pressure would be predicted to rise by 17 mm. Hg when he increased in weight from 140 to 210 pounds. The actual observations in our own series, relating to a weight increase of this order, implied a rise in mean pressure of 21 mm. Hg (that is, from 124/74 to 149/91 mm. Hg for a man having an average arm circumference and fatness). The observed and predicted rises in pressure are not grossly dissimilar.

Finally, what part does cholesterol play in the ill effects of obesity? The results of this study show that the level of serum cholesterol rises with age but is not related to the level of blood pressure, obesity, or body weight. These topics have been discussed elsewhere.[3] If it is accepted that obesity or, rather, overweight predisposes to the development of coronary artery disease, then the evidence would force us to favor the "blood pressure" rather than the "cholesterol" school in the controversial matter of the pathogenesis of arterial disease. However, it is conceivable that the life-long bathing of arterial walls in serum containing high concentrations of cholesterol—which is a feature of our Western civilization—gradually impairs the volume-elasticity characteristics of the main arterial reservor. This could be a factor in the association of a rising blood pressure with advancing age and with increasing body weight, both of which are prominent among Australians, whose average serum cholesterol concentration exceeds 200 mg. per cent, but absent among natives of New Guinea whose cholesterol level is only 130 mg. per cent.[11]

The conclusion is that blood pressure is related to weight or bulk of the body, but not to obesity except insofar as it contributes to bulk. To outgrow one's aorta might be one of the dangers of overeating.

Summary

Measurements were made in 100 men, 20 to 40 years of age, of blood pressure, height, weight, skinfold thicknesses, circumference of the arm, and serum cholesterol.

Analysis showed a positive correlation between blood pressure and body weight, other factors being held constant. Obesity (judged by the thickness of subcutaneous fat) had no apparent influence on blood pressure except insofar as it affected the total body weight. Serum cholesterol concentration was related to age, but not to body weight or obesity.

An increase in body weight of 28 pounds, without any change in arm circumference, was associated with an increase of 10 mm. Hg systolic and 7 mm. Hg diastolic pressure.

The contrast between these results and observations among natives in New Guinea are discussed briefly and a possible explanation is suggested.

Acknowledgment

I am grateful to the Red Cross Blood Transfusion Service for cooperation in this study, to Dr. C. L. Hamblin, of the Department of Humanities, University of New South Wales, for assisting with the mathematical analyses, and to Miss Iris Yee for technical assistance.

Summario in Interlingua

Esseva effectuate—in 100 masculos de etates de inter 20 e 40 annos—mesurationes del pression de sanguine, del altor, del peso, del spissitate de plicas cutanee, del circumferentia brachial, e del cholesterol del sero.

Le analyse del datos revelava un correlation positive inter le pression de sanguine e le peso del corpore (con le altere factores tenite a nivellos constante). Obesitate—in tanto que

reflectite in le spissatate del grassia subcutanee—exerceva nulle apparente influentia super le pression de sanguine, excepte via su effecto super le total peso corporee. Le concentration del cholesterol seral esseva relationate al etate del subjectos sed non a lor peso corporee o a lor obesitate.

Un augmento del peso corporee per 28 libras—non accompaniate de un alteration del circumferentia brachial—esseva associate con un augmento de 10 mm de Hg in le pression systolic e de 7 mm de Hg in le pression diastolic.

Le contrasto inter iste resultatos e observationes in nativos de Nove Guinea es discutite brevemente. Un explication possibile de iste contrasto es suggerite.

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The records of 500 autopsied patients who died with acute myocardial infarction were reviewed with particular attention to the age of menopause in the young women in this series. Of the 16 women who died with acute myocardial infarction before the age of 53, 14 had reached the menopause. In a control group only 6 of 13 women of nearly similar age had reached menopause—a statistically significant difference. The authors conclude that the data indicate that young women who die with acute myocardial infarction usually have had an early menopause and that, therefore, some factor associated with the menstrual cycle possibly protects young women against acute myocardial infarction.

Sagall

Clinical and Physiologic Relationships in Mitral Valve Disease

By Philip Samet, M.D., Robert S. Litwak, M.D., William H. Bernstein, M.D., Eugene M. Fierer, M.D., and Leonard M. Silverman, M.D.

Physiologic data obtained during right and combined right and left heart catheterization are presented in a variety of subjects with mitral valve disease. These studies have led to a broader understanding of the pathophysiology of this disease. The clinical value of combined heart catheterization is illustrated.

MUCH has been written relative to the physiologic abnormalities produced by mitral stenosis and insufficiency. Most of the data and the concepts derived therefrom have been obtained by right heart catheterization.[1-8] The introduction of left heart and combined heart catheterization[9-19] has greatly enhanced the value of physiologic study in patients with rheumatic mitral valve disease and has permitted a reevaluation of the concepts previously developed.

The major purpose of the present report is to delineate and separate the varied types of rheumatic mitral valve disease and to illustrate the importance of combined simultaneous right and left heart catheterization. Evaluation of some of the clinical and physiologic effects of mitral commissurotomy are also presented.

Methods and Materials

Fifty-three subjects with varied types of mitral valve disease were studied. The physical characteristics and diagnoses are given in table 1.* Multivalvular disease was present in 13 subjects. Fifty-one of the 53 patients had symptoms at the time of study. The complaints included dyspnea at rest or on exertion, orthopnea, weakness and easy fatigability, cough with or without hemoptysis, palpitation, and edema. Gross heart failure, left or right, was not present in any subject at the time of study. The majority had been digitalized prior to catheterization. Several were digitalized during or subsequent to the first study. There was no clinical evidence of active rheumatic fever or subacute bacterial endocarditis noted in any of these subjects.

Each subject had a complete history, physical examination, cardiac fluoroscopy, and electrocardiogram performed prior to physiologic study. Laboratory studies included prothrombin time, bleeding and clotting time, and platelet count in addition to the usual determinations. The hematologic work-up was especially required prior to left heart catheterization. All subjects were hospitalized for a sufficient period of time prior to catheterization to permit attainment of the maximum possible cardiac compensation.

Right heart catheterization and arterial cannulation were performed via the same arm (whenever possible), in the usual manner in the basal postabsorptive state to permit cardiac output determination by the Fick principle. Multiple steady-state pressure and cardiac output determinations were made at rest and during exercise and recovery. When feasible, double-lumen or triple-lumen catheters were employed to permit simultaneous pressure recording from multiple sites in the pulmonary artery and right heart. With the right heart catheter and brachial artery needle in situ, the patient was then turned to the prone position. Repeat right heart pressures were obtained, followed by the intramuscular administration of 50 to 75 mg. of meperidine hydrochloride.

Left heart catheterization was carried out by a modification of the technic of posterior percutaneous puncture of Fisher,[12] subsequent to fluoroscopic visualization of the left atrium in the prone position. Two 6 to 8 inch no. 17 thin-walled styletted needles were inserted in the left atrium. Polyethylene tubing was then passed through these

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*Tables 1, 2, and 3 have been omitted from the published paper at the request of the editor. These tables are available in mimeograph form from the authors on request.

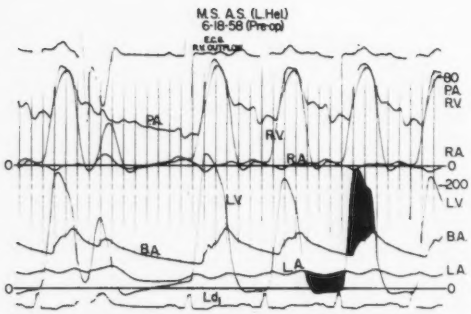


FIG. 1. Simultaneous right atrial, right ventricular, pulmonary artery, left atrial, left ventricular, and brachial artery pressure curves in a 34-year-old white woman with aortic and mitral stenosis. The *shaded areas* represent the mean systolic left ventricular-brachial artery, and mean diastolic left atrial-left ventricular gradients. A standard lead and a right ventricular endocardial lead are also shown.

needles into the left atrium and left ventricle. Simultaneous pressures were obtained (from the same baseline and at identical strain-gage sensitivities[20]) from the left atrium, left ventricle, and brachial artery.

In selected subjects the left heart needles were then removed over the catheters leaving the latter in situ, i.e., in the left atrium and left ventricle. The patient was then returned to the supine position. After a suitable rest period to permit reestablishment of the steady state, repeat measurements of right and left heart pressures and cardiac output were performed at rest and during exercise and recovery in this group.

All pressure measurements were initially made on a 6-channel* photographic recorder employing Statham P23AA, P23D, and P23G strain gages. More recently, an 8-channel* photographic recorder has permitted simultaneous recording of right atrial, right ventricular, pulmonary arterial, left atrial, left ventricular, and systemic arterial pressures (fig. 1). Blood gas analysis was performed by standard technics on a Van Slyke manometric apparatus. Expired gas analyses were performed with a Scholander gas analyzer.

In a few subjects left heart catheterization was done via the bronchoscopic approach.

Initially, left heart catheterization data were obtained only in the prone position. In the midperiod of this study, patients were returned to the supine position whenever possible. More recently, such exercise studies in the supine position were scheduled only when gradients of questionable significance were noted in the prone position.

*Electronics for Medicine, White Plains, N.Y.

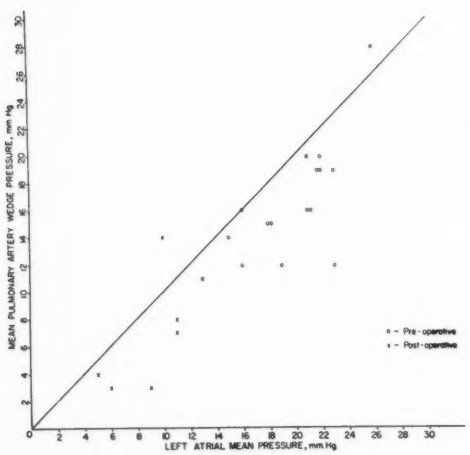
In the supine and prone positions, the selected reference level for right heart pressures was 5 cm. dorsal to the angle of Louis; the corresponding level for left heart pressures was 10 cm. dorsal to this angle.

Left atrial and left ventricular pressures were determined simultaneously in the operating room immediately prior to and subsequent to mitral commissurotomy. The zero level was 10 cm. posterior to the angle of Louis. The left-sided chamber pressures were recorded via a 1½-inch no. 20 gage needle, 48 inches of black polyvinyl tubing, and Statham P23AA strain gages.

RESULTS

The pressure data obtained in the course of these studies are given in table 2. The cardiac output data are outlined in table 3. These data permit evaluation of a number of relationships.

The pulmonary artery wedge pressure has been employed widely as a measure of left atrial pressure.[21–23] The relation between these 2 pressure levels in 22 patients is illustrated in figure 2. The pulmonary artery wedge pressure was determined at the onset of right heart catheterization, supine. The left atrial pressure was determined during combined right and left heart catheterization after return to the supine position. A straight line drawn at an inclination of 45° represents the theoretical line of identity. Most points fall to the right of the 45° line. The average pulmonary artery wedge pressure is 14 mm. Hg; the average left atrial mean pressure is 17 mm. Hg. The average difference, regardless of the sign, is 3.5 mm. Hg. This would suggest that the mean pulmonary artery wedge pressure gives a fair approximation of mean left atrial pressure and, by inference, an approximation of the degree of narrowing of the mitral valve. In figure 3 the mean pulmonary artery wedge pressure is plotted on the ordinate. The corresponding left atrial-left ventricular mean diastolic gradients are plotted on the abscissa. The numbers at any one level of pulmonary artery wedge pressure refer to the prone and supine gradients in patients 1, 2, 3, etc. Figure 3 readily demonstrates the poor correlation between these variables. If the upper limit of normal wedge



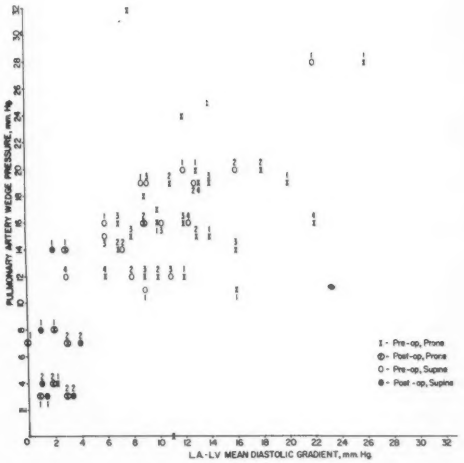


FIG. 2 *Left.* Pulmonary artery wedge pressure (*ordinate*) is plotted against the mean left atrial pressure supine (*abscissa*). The *straight line* is the 45° line of identity. The pressures in this and succeeding figures are all in mm. Hg.

FIG. 3 *Right.* Pulmonary artery wedge pressure (*ordinate*) is plotted against the mean diastolic left atrial-left ventricular gradient, prone or supine. The small numbers at any one level of *ordinate* represent single cases. The effect of a change in position, from prone to supine, upon the gradient is thus illustrated. For example, at a wedge pressure of 12 mm. Hg, the gradients prone and supine are shown for 3 patients (2, 3, and 4).

pressure is taken as 12 mm. Hg, it appears that significant gradients are present in 5 subjects with normal wedge pressures. Dickens et al. have observed similar findings.[24]

The effect of position upon the left atrial-left ventricular gradient is worthy of comment. The average gradient prone in 25 patients (before and after operation) at rest prone was 10 mm. Hg. In these same subjects the mean gradient at rest supine equaled 7 mm. Hg. During exercise in the supine position, the gradient rose to 12 mm. Hg. Similar data were available in 15 preoperative studies. These latter gradients averaged 14 mm. Hg at rest prone, 10 mm. Hg at rest supine, and 18 mm. Hg during exercise supine.

Position, prone or supine, has also been found to have a definite effect on pulmonary artery pressure (fig. 4). The abscissa is the mean pulmonary artery pressure, supine, during right heart catheterization only. The corresponding pulmonary artery mean pressures prone (during right and during combined heart catheterization) and during combined heart catheterization supine, are shown on the ordinate. The numbers at any one level of pulmonary artery mean pressure, supine, right heart catheterization only, refer to the pulmonary artery mean pressures during combined heart catheterization (prone or supine) and during right heart catheterization, prone, in patients 1, 2, 3, etc. The great majority of the points fall above the 45° line of identity.

The relationship between cardiac index and the mean diastolic left atrial–left ventricular gradient at rest and exercise during combined heart catheterization is pictured in figure 5. The preoperative and postoperative cases are readily separated in this fashion, except for 2 patients, A. Gre. and W. Cur. The former is a 30-year-old asymptomatic white woman, the latter a 36-year-old white man in whom the myocardial factor was considered to be the primary cause of the patient's symptomatology. The gross increase in gradient induced by relatively small increases in flow (and potentiated by the concomitant tachy-

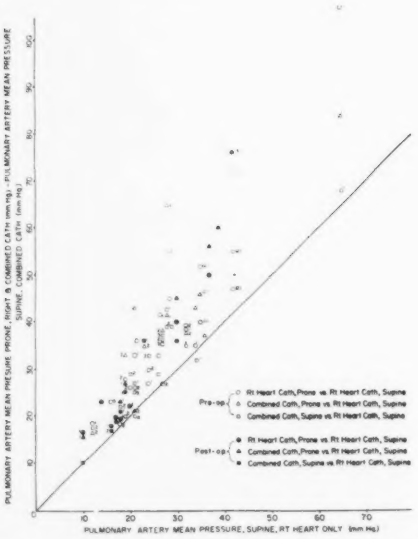


FIG. 4. Pulmonary artery mean pressure during right heart catheterization only, supine, plotted against the corresponding pressure prone, before and after insertion of the left heart needles, and against the pulmonary artery mean pressure, supine, during combined heart catheterization. The *straight line* is the 45° line of identity. Note that most points fall above the line. The small numbers at any one level of the *abscissa* refer to individual cases as in figure 3.

cardia of exercise) is easily noted in the preoperative cases with mitral valve block.

Oxygen consumption at rest and during exercise is plotted against the left atrioventricular gradient in figure 6. There was no overlap between the preoperative and postoperative studies, again except for A. Gre. and W. Cur. On the other hand, a plot of cardiac index against oxygen consumption at rest and exercise during combined heart catheterization revealed considerable overlap between the preoperative and postoperative subjects.

The effect of mitral commissurotomy upon cardiac index is listed in table 4 in 12 subjects. The data of S. Bri. have been eliminated from the average data because gross mitral insufficiency was produced at surgery in this patient. In 5 subjects a significant rise in output followed commissurotomy; in 6 subjects the output remained unchanged. Comparison of the oxygen consumption values in the 2 states, i.e., before and after operation, reveals virtually identical figures, 119 and 122 ml./min./M.^{2} respectively. The average difference in oxygen uptake, regardless of the sign of the deviation, is 8 ml./min./M.^{2}

A comparison of the mean left atrial-left ventricular diastolic gradient obtained in the course of combined heart catheterization with those available at the operating table is provided in table 5. In the prone position the mean gradient for 13 patients was 13.5 mm Hg. The corresponding figure for the preoperative operating room gradient was 14.7 mm. Hg. In the supine position, the gradient averaged 10 mm. Hg in 8 subjects, in whom these data were available. In these same 8 subjects, the gradient in the prone position was 12 mm. Hg; the operating room average gradient was 15 mm. Hg.

DISCUSSION

The development of left and combined heart catheterization has permitted a more comprehensive view of the hemodynamic abnormalities resulting from mitral valve disease and also a firmer basis upon which to evaluate the results of mitral commissurotomy. The physiologic hallmark of mitral stenosis is the existence of a significant mean diastolic left atrial-left ventricular gradient. Gradients of 8 mm. Hg at rest prone, 5 mm. Hg at rest supine, and 10 mm. Hg during exercise supine have, somewhat arbitrarily, been defined as the minimal gradients suggestive of physiologically and clinically significant mitral stenosis. These levels were chosen after due study of the postoperative gradients obtained in subjects with good to excellent symptomatic improvement after surgery.

Pulmonary artery wedge pressure (upper level of normal 12 mm. Hg) has been utilized as a measure of mean left atrial pressure and also as a measure of the presence or absence of physiologically significant mitral valve block. The data in the present study raise serious doubt as to the validity of such an approach. Not only may wide variations occur in individual cases in the level of mean pul-

TABLE 4.—*Cardiac Index before and after Mitral Commissurotomy*

Patient	Before operation		After operation	
	Cardiac index (L./min./M.²)	O_2 consumption (ml./min./M.²)	Cardiac index (L./min./M.²)	O_2 consumption (ml./min./M.²)
S. Bri.	2.50	111	1.85	104
L. Van.	2.50	125	2.87	139
D. Dix.	1.92	127	2.21	120
R. Ros.	3.17	120	3.81	121
S. Wor.	1.92	128	2.51	125
L. Kar.	2.33	118	2.43	125
S. Jon.	2.32	136	2.35	115
R. Ros.	1.99	107	1.91	119
S. Tal.	1.91	102	1.86	104
G. Doy.	2.37	107	2.73	120
M. Mul.	1.91	111	1.95	119
R. Rie.	2.54	129	2.62	133
Average (excluding S. Bri.)	2.26	119	2.48	122

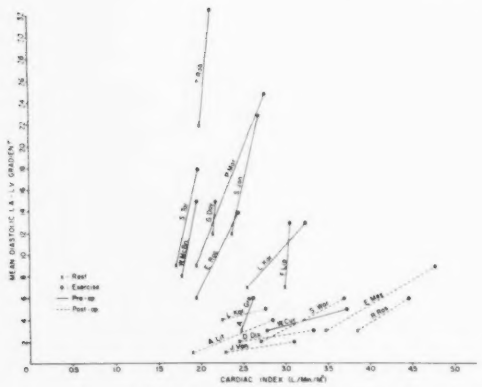
Average difference (excluding S. Bri.)
Cardiac index: 0.24 L./min./M.²
O_2 consumption: 8 ml./min./M.²

TABLE 5.—*Comparison of Preoperative Catheterization and Operating Room Mean Diastolic Atrioventricular Gradients*

Patient	Preoperative		In operating room
	Prone	Supine	
E. Ros.	10	6	13
E. Coo.	9	11	10
A. Dan.	8	—	15
D. Dix.	11	13	15
R. Ros.	18	16	23
S. Wor.	24	—	16
L. Kar.	7	7	9
W. McB.	10	8	19
F. Lip.	14	7	18
J. Gay.	15	—	15
G. Doy.	20	12	13
R. Vog.	13	—	10
R. Cos.	17	—	15
Average (all 13)	13.5		14.7
Average (8)	12	10	15

monary artery wedge and mean left atrial pressure (fig. 2), but even more fundamental is the fact that significant left atrioventricular diastolic gradients may coexist with normal pulmonary artery wedge pressures (fig. 3). The existence of tight mitral stenosis has been surgically verified in 3 of these subjects with normal pulmonary artery wedge pressures, E. Coo. and W. McB. in table 2, and a third subject not listed in tables 1 to 3. Furthermore, an elevated pulmonary artery wedge pressure was found 10 months postoperatively in D. Dix.; left atrial mean pressure was normal at this time and the gradients at rest were 2 and 1 mm. Hg prone and supine respectively. Substitution of pulmonary artery wedge mean pressure for left atrial mean pressure, as is still being done, is thus fraught with considerable potential error.

The finding that mean pulmonary artery wedge pressure may be recorded as lower than mean left atrial pressure (fig. 2) requires comment. At first thought, this observation is difficult to understand. The fact that the zero baseline for the pulmonary artery wedge pressure is taken as 5 cm. dorsal to the angle of Louis while that for the left atrial pressure supine is taken as 10 cm. dorsal to this point does not explain the difference in pressures. Actually, pulmonary artery wedge pressure is recorded in an "unsteady state" at the onset of right heart catheterization in this laboratory. A large L-shaped lead shield (to protect the operator from stray x-ray radiation) is still in situ on the fluoroscopic table at this time. The patient's arm rests in the angle of this shield. The room lights have just been turned on after positioning the catheter in the wedge position. The wedge pressure is recorded as rapidly as possible and the catheter tip withdrawn to the right or left pulmonary artery to prevent any complications from the wedging procedure. Simultaneously recorded pulmonary artery pressures and ventricular rates are usually significantly higher at this point than the corresponding values obtained later in the study when the tip is withdrawn to the pulmonary artery and a steady state is achieved. These findings suggest that the true steady-state pulmonary artery wedge pressures would be lower than those in figure 2, and that the differences between steady-state wedge pressures and steady-state left atrial pressures su-



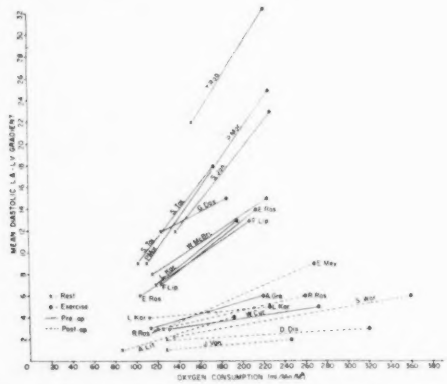


FIG. 5 *Left.* The relation between atrioventricular gradient and cardiac index at rest and during exercise (supine) in the course of combined heart catheterization. The preoperative and postoperative cases are clearly separated except for A. Gre. and W. Cur.

FIG. 6 *Right.* Relationship between atrioventricular gradient and oxygen consumption at rest and during exercise. Data obtained during combined heart catheterization.

pine would be even greater than those noted in figure 2. It is our belief that the recording of pulmonary artery wedge pressure is subject to considerable actual and potential error and that the best explanation for the differences in figure 2 is to be found in consideration of these errors. This problem will be discussed more fully elsewhere.[33] The fact that cardiac output at rest and exercise, during combined heart catheterization supine, agreed closely with those during right heart catheterization alone[31] suggests that the clinical condition of the patient had not deteriorated at the time of combined heart catheterization and that the difference between left atrial and pulmonary artery mean wedge pressures could not be ascribed to such deterioration.

Since different laboratories perform left heart catheterization in varying positions (supine in the bronchoscopic, direct left ventricular, and suprasternal approaches, and prone in the percutaneous transthoracic technic of Fisher), analysis of the effect of a change in position upon the mean diastolic left atrial-left ventricular gradient and upon pulmonary artery pressure is of considerable interest. The gradient is 3 mm. Hg larger in the prone than in the supine position for all cases (before and after operation) and 4 mm. Hg greater in the preoperative cases. Change in position, i.e., prone or supine, also results in a change in pulmonary artery pressure. The effects of left heart catheterization per se and of change in position from supine to prone and back again to supine are shown in figure 4. In 31 subjects mean pulmonary artery pressure was measured in the supine position and again in the prone position before insertion of the left atrial needles. The average pressure supine was 26 mm. Hg, the average pressure prone, 35 mm. Hg. The difference is significant, $p<.001$. The 95 per cent confidence interval is 6 to 12 mm. Hg. In 13 patients, the mean pulmonary artery pressure in the prone position before insertion of the left heart needles averaged 41 mm. Hg; after insertion of the needles the mean pressure rose only to 44 mm. Hg; this difference is not statistically significant, $.3>p>.2$. The 95 per cent confidence interval is -3 to $+8$ mm. Hg. Left heart catheterization per se caused an insignificant rise in pulmonary artery pressure. In 20 studies mean mean pulmonary artery supine was 30 mm. Hg. Rotation into the prone position and insertion of the left heart needles resulted in a rise of 15 mm. Hg to 45 mm. Hg, $p<.001$. The 95 per cent confidence interval is 10 to 20 mm. Hg. In 11 subjects mean pulmonary artery pressure prone after insertion of the left heart needles was 39 mm. Hg. This pre-

sure level fell to 30 mm. Hg after rotation back into the supine position, $.01>p>.001$. The 95 per cent confidence interval is 4 to 15 mm. Hg. This again demonstrates the tendency of the prone position to cause a rise in pulmonary artery pressure. In 26 patients mean pulmonary artery pressure supine (during right heart catheterization alone) was 25 mm. Hg; after rotation into the prone position, insertion of the left heart needles, and rotation back to the supine position, the same pressure averaged 30 mm. Hg, $p<.001$. The 95 per cent confidence limit is 3 to 7 mm. Hg. This represents a rise of only 5 mm. Hg, compared to a rise of 15 mm. Hg in the group of 20 subjects referred to above.

At least part of the increase in pulmonary artery pressure and in left atrial-left ventricular mean diastolic gradient in the prone as opposed to the supine position may be ascribed to the increased ventricular rate in the prone position. The pernicious effect of tachycardia in patients with mitral stenosis is well known. The diastolic period of atrioventricular filling is shortened during tachycardia. This necessitates an increased rate of flow across the mitral valve in the shortened diastolic period if cardiac output is to be maintained. An increased rate of flow in turn necessitates a greater diastolic pressure gradient across the valve. Such an increase leads to further left atrial, pulmonary venous, and pulmonary artery hypertension. This effect is especially noted in patients with atrial fibrillation. The gradient is larger following a short R-R electrocardiographic interval, and progressively falls in the diastolic period between a prolonged R-R interval. In addition to a rise in left atrioventricular diastolic gradient and rise in pulmonary artery pressure (often with a rise in right ventricular end-diastolic pressure), the prone position was associated with the development of a cyanotic suffusion of the face, neck, and upper chest. This physical sign was noted only in the patients with mitral valve block, but was not invariably found in these patients. Attempts to reproduce this sign in bed on the board proved unsuccessful, however.

The importance of interrelations between heart rate, cardiac output, and diastolic atrioventricular gradient has been emphasized by many investigators. The graphic relation between mitral valve flow and mean diastolic gradient is illustrated in figure 5. There is a clear delineation between the preoperative and postoperative cases except for the asymptomatic, A. Gre. and for W. Cur. Mitral valve block results in a sharp rise in gradient for relatively small increases in blood flow.

The details of multiple hemodynamic studies in 2 patients (J. Van. and D. Dix.) are outlined in figures 7 and 8. Each was catheterized prior and subsequent to a successful mitral commissurotomy. The progressive fall in pulmonary artery pressure postoperatively is probably secondary to progressive regression of pulmonary vascular disease. In J. Van. the result was a completely normal pulmonary artery pressure at rest and exercise 1 year after surgery. In D. Dix., 5 weeks after surgery, moderately severe pulmonary hypertension persisted at rest and during exercise. Without simultaneous left heart catheterization, the persistent pulmonary hypertension could have been attributed to inadequate mitral commissurotomy. However, the small left atrial-left ventricular diastolic gradients at rest and exercise obtained at this time render such an explanation invalid. The all but complete abolition of the left atrial-left ventricular gradient after surgery, both at rest and during exercise, in both patients, is worthy of note.

The effect of mitral commissurotomy upon cardiac output has been extensively discussed in the literature. Two recent papers[8,25] illustrate the problem of interpretation of output changes. Donald and co-workers[8] determined cardiac outputs in 28 patients before and after mitral commissurotomy. In 26 these data were available prior to and after surgery. The average index preoperatively was 2.87 L./min./M.^{2} (a rather surprisingly normal level). The postoperative average was 2.24 L./min./M.^{2} This fall occurred despite pronounced clinical improvement postoperatively in 24 of the 28 subjects. Inspection of

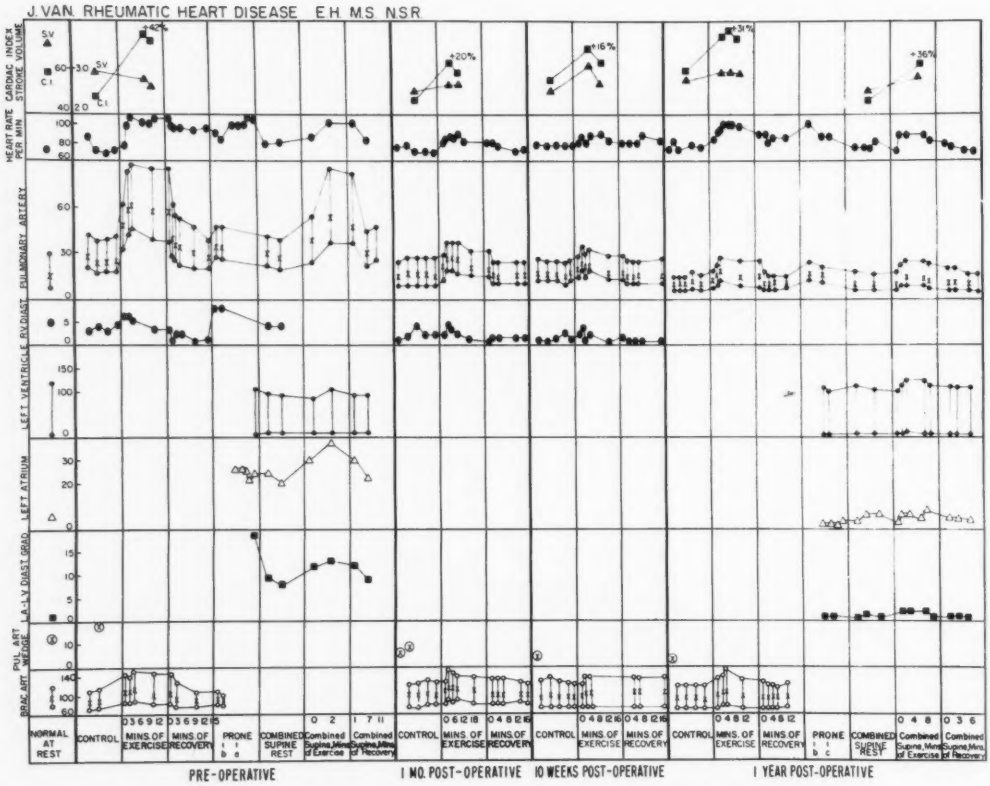


FIG. 7. Preoperative and postoperative data in J. Van. (*b* and *c* under *prone*) refer to data in the prone position prior to and after insertion of the left heart needles.

the oxygen consumption figures, however, provides at least a partial explanation for the fall in output after commissurotomy. The average oxygen consumption preoperatively was 154 ml./min./M.^{2}; the corresponding postoperative figure was 130. The average change (disregarding the sign of the change) is 26 ml./min./M.^{2} In view of this large fall in oxygen consumption, comparison of preoperative cardiac indices is difficult. On the other hand, Dickens and co-investigators[25] noted an average cardiac index of 2.17 L./min./M.^{2} in 13 patients prior to surgery. The output rose to 3.00 L./min./M.^{2} after surgery. The preoperative oxygen consumption was 171 ml./min./M.^{2}; the corresponding postoperative figure was 184 ml./min./M.^{2} The average change was 25 ml./min./M.^{2} At least part of the output rise after surgery must be attributed to an increase in oxygen consumption. Other workers have noted variable increases in flow after surgery.

Eleven output studies before and after operation are available in the present paper. In half, a significant increase in cardiac index occurred; in the other half the output was unchanged. The average increase in flow was about 10 per cent (table 4). The average oxygen uptake prior to surgery was 1 9 ml./min./M.^{2}; postoperatively the oxygen consumption was 122. The average change, regardless of the sign of the change, was 8 ml./min./M.^{2} The series is too small, however, to permit definite conclusions.

In view of the acknowledged importance of flow and heart rate in interpretation of a

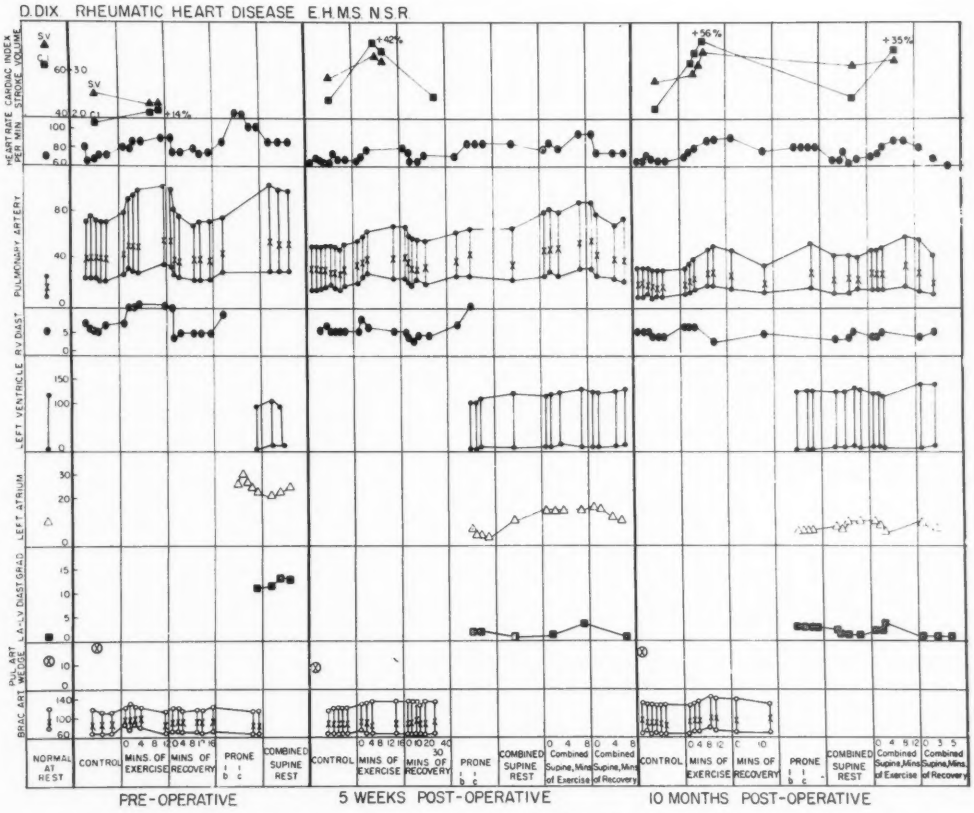


FIG. 8. Preoperative and postoperative data in D. Dix. (*b* and *c* under *prone*) have the same significance as in figure 7.

diastolic atrioventricular gradient, the fairly close agreement between the catheterization and operating room gradients (table 5) is somewhat surprising. The scatter in agreement is wide, but the average gradient prone during catheterization of the left heart is of the same order of magnitude as that during surgery. The smaller gradients obtained in the supine position during catheterization again indicate that a more basal state is achieved in this position than in the prone position.

In 2 subjects acute digitalis studies were performed during the first catheterization. In subjects the initial cardiac catheterization was performed in the undigitalized state and repeated within 1 to 2 weeks after continued digitalization. The results are of interest with regard to the possible role of the myocardial factor[6, 26] in the production of the abnormal hemodynamic findings in mitral stenosis. Acute digitalization (during the catheterization study) in A. Dan. (cath. no. 9) resulted in a distinct fall in pulmonary artery pressure, from 73/43,55 mm. Hg to 60/28,43, and a 12 per cent increase in cardiac index despite an 8 per cent fall in oxygen consumption (tables 2 and 3). The arteriovenous oxygen difference fell from 7.6 to 6.2 volumes per cent. Digitalis was continued for more than 1 week, and catheterization was repeated. A further fall in pulmonary artery pressure to 54/27,35 mm. Hg was noted. On left heart catheterization the left atrioventri-

cular gradient was 8 mm. Hg prone. No evidence of left ventricular failure was noted. At surgery the gradient was 15 mm. Hg before commissurotomy, proving the existence of mitral valve block. F. Lip. was digitalized between the first and second of 3 preoperative cardiac catheterizations. Digitalization was followed by a distinct fall in pulmonary artery pressure. Cardiac output fell slightly (tables 2 and 3). At left heart catheterization (after digitalization) a 14 mm. Hg gradient was found in the prone position. No evidence of left ventricular failure was noted. At surgery the precommissurotomy gradient equaled 18 mm. Hg, again proving the existence of mitral valve block. In 3 other subjects (tables 1 to 3)), digitalization resulted in no significant change in right heart hemodynamics or cardiac output.

The hemodynamic data in A. Dan., and F. Lip. noted above demonstrate that mitral valve block and myocardial weakness may at least coexist despite an improvement in physiologic data after acute or chronic digitalization. Such changes do not necessarily indicate the primacy of the myocardial factor in the production of symptomatology and cardiac enlargement. Both patients have had surgically proved mitral stenosis and an excellent response to mitral commissurotomy. Combined right and left heart catheterization was of great value in differentiating the causes of pulmonary hypertension in these patients. This has been discussed more fully elsewhere.[27]

An intensive search has been made for patients illustrative of the myocardial factor. To date only 1 and possibly 2 examples have been found. In theory, the absence of a significant left atrial-left ventricular mean diastolic gradient both at rest and during exercise is a necessary prerequisite for the diagnosis of the primacy of the myocardial factor. Previous definitions based on the absence of significant pulmonary hypertension at rest or exercise during right heart catheterization alone[6, 26] are inadequate, since significant diastolic atrioventricular gradients have been found in patients (E. Coo., L. Kar., and S. Ber.) with only minimal pulmonary hypertension at rest or exercise during right heart catheterization alone. In E. Coo. and L. Kar. surgical confirmation of the diagnosis has been obtained. The physiologic data in W. Cur. point to the importance of the myocardial factor. The mean diastolic left atrial-left ventricular gradient was 4 mm. Hg prone, 3 mm. Hg supine at rest, and 5 mm. Hg during exercise. The patient's main complaints were weakness, easy fatigability, and exertional dyspnea. On physical examination a mitral opening snap and apical diastolic rumble with presystolic accentuation were audible. The electrocardiogram was atypical in that left bundle-branch block was found. The patient has been subsequently followed for 15 months and has been in clinical failure on several occasions. This patient has therefore been classified in the group wherein the myocardial factor rather than mitral valve block is responsible for the clinical, physical, and laboratory abnormalities. Surgical confirmation has, of course, not been obtained.

V. Whi. was a 37-year-old white woman who possibly, but not certainly, fell into this same category of the myocardial factor. The left atrial-left ventricular gradient was minimal at rest prone (during normal sinus rhythm) during left heart catheterization on 2 separate studies. During the second left heart study, nodal tachycardia developed with a rate about 140; the gradient thereupon rose to 10 mm. Hg prone, and 13 mm. Hg supine. Significant pulmonary hypertension was absent during both rest and exercise on 2 occasions during right heart catheterization. It is difficult to be certain just how to classify this patient. No other examples of the myocardial factor have been observed in this laboratory.

The studies available in J. Gla., a 34-year-old white man, illustrate the problem of recurrent mitral stenosis after commissurotomy.[28] In 1950 he was catheterized elsewhere* before and subsequent to mitral valve surgery. The pulmonary artery pressure was 74/49, 54 mm. Hg, preoperatively. The postoperative mean pulmonary artery pressure was 31 mm. Hg at rest. The preoperative

*In the laboratory of Dr. L. Dexter, in Boston, Mass.

TABLE 6.—*Comparison of Cardiac Output Data during Right Heart Catheterization Alone with Those Subsequent to Removal of the Bronchoscope (PB)*

Patient	Cardiac index (L./min./M.²) Rt.	PB	A-V diff. (vol. %) Rt.	PB	Oxygen consumption (ml./min./M.²) Rt.	PB	Respiratory quotient (R) R	PB
J. Gay.	2.50	2.45	6.0	6.2	151	152	.85	.75
N. Ber.	1.76	1.56	7.1	8.7	124	135	.79	.69
B. Wei.	2.53	3.30	4.9	4.4	124	145	.93	.77
E. Gec.	2.19	2.51	5.3	4.6	117	115	.87	.62
F. Eul.	2.53	2.99	5.2	5.1	133	153	.69	.48
Average	2.30	2.56	5.7	5.8	130	140	.83	.66
Average difference	.36		.6		11		.16	

cardiac index was 2.1 L./min./M.² (oxygen consumption 153 ml./min./M.²); this rose to 3.2 L./min./M.² (oxygen consumption 139 ml./min./M.²) shortly after surgery. Six and one half years later pulmonary artery pressure had risen to 61/35, 42 mm. Hg. Cardiac index had fallen to 1.52 L./min./M.²). Left atrial mean pressure prone was 32 mm. Hg at this time, and the diastolic atrioventricular gradient was 22 mm. Hg. Restenosis had evidently developed in the period between 1950 and 1956. A second commissurotomy was refused by the patient. His course was progressively downhill. At postmortem examination 5 months later, tight mitral stenosis was found.

Hemodynamic studies are available in 2 asymptomatic subjects with mitral stenosis. Both had typical physical findings of mitral stenosis. The left atrium was enlarged in both patients. The electrocardiogram exhibited P-wave abnormalities in both subjects, but no evidence of right or left ventricular hypertrophy. In the first patient, R. Sch., the pulmonary artery pressures were normal at rest, but slight pulmonary hypertension appeared during exercise. Cardiac index was normal at rest with an increase on exercise which was at the lower limits of normal. A. Ire., the other asymptomatic patient with mitral stenosis, was catheterized twice in the undigitalized state. The first was a combined right and left catheterization, the second a right heart catheterization. Mild pulmonary hypertension developed during exercise in both studies. The maximum mean diastolic left atrial-left ventricular gradient during exercise was 6 mm. Hg. Cardiac index was slightly depressed during the first study but was normal on the second occasion. There is little doubt that abnormal hemodynamic data may be found in at least some asymptomatic subjects with mitral stenosis.

As has recently been reemphasized by Brachfeld and co-workers,[29] left heart catheterization may be of prime importance in the diagnosis of occult mitral stenosis. T. Rob., a 42-year-old white man, was severely disabled with exertional dyspnea and peripheral edema. Despite signs of right ventricular hypertrophy and probable pulmonary hypertension on physical examination, a mitral diastolic rumble was not present, although a soft diastolic blow was noted at the base. The electrocardiogram suggested atrial hypertrophy with marked right ventricular hypertrophy. The resting pulmonary artery pressure was 104/42, 65 mm. Hg. Left heart catheterization demonstrated atrial hypertension and a large atrioventricular gradient, 26 mm. Hg at rest. The diagnosis of very tight mitral stenosis was subsequently verified at surgery. Similar cases have been reported by others.[30]

Left heart catheterization was performed by the bronchoscopic technic in 5 patients in whom cardiac output data were available prior to and subsequent to insertion and removal of the bronchoscope. At least 30 minutes elapsed between removal of the bronchoscope, and the postbronchoscopic outputs. The results are given in table 6. Gross differences in cardiac index and associated data are pres-

TABLE 7.—*Comparison of Cardiac Output Data during Right Heart Catheterization Alone with Those during Combined Heart Catheterization by the Posterior Percutaneous Technic (24 Cases)*

	Cardiac index (L./min./M.²)		A-V diff. (vol. %)		Oxygen consumption (ml./min./M.²)		Respiratory quotient	
	Right	Combined	Right	Combined	Right	Combined	Right	Combined
Average	2.48	2.45	5.2	5.3	123	124	.80	.82
Average difference	.17		.4		8		.05	

ent in 4 of the 5 patients. The averaged values vary considerably and the averaged differences are large. The corresponding data[31] from output comparison (in 24 patients) of right and combined heart catheterization by the posterior percutaneous puncture technic is shown in table 7. In this laboratory the steady state is more readily achieved after left heart catheterization by the posterior percutaneous technic than by the bronchoscopic technic. In the only other comparison of cardiac output during right heart catheterization alone and during left or combined heart catheterization available in the literature to date, Morrow and co-workers[32] noted a cardiac index of 3.05 and 2.26 L./min./M.² during right and during left heart catheterization respectively. The average difference in output in their 8 subjects was 0.86 L./min./M.² This variation is considerably larger than in the series of 24 patients referred to above.

These clinical and physiologic experiences in patients with mitral valve disease have led to a classification of mitral stenosis based upon the presence or absence of a left atrioventricular gradient. In the asymptomatic patient with mitral stenosis, demonstration by left heart catheterization of an absent or small gradient at rest or exercise certainly indicates that the degree of block is of little clinical or physiologic import at the moment. The demonstration of a significant gradient (as defined early in this paper) at rest or during exercise in the asymptomatic subject may in the future by a clear-cut indication for mitral commissurotomy. At present, the question of surgical intervention in such a patient remains a moot point, which may be decided by the ancillary electrocardiographic and fluoroscopic findings. It should be noted, however, that many patients realize the magnitude of their preoperative disability only after relief thereof by surgery.

In a similar fashion, symptomatic patients with pure mitral stenosis can be divided into 2 groups. Those with significant gradients during left heart catheterization obviously require commissurotomy in the absence of a clear-cut contraindication. The symptomatic patient with a small or absent gradient at rest or exercise probably falls into the category of the myocardial factor and should not be subjected to surgery. These patients can be detected only with left heart catheterization.

The complications of left heart catheterization deserve discussion. To date 120 combined right and left heart catheterizations have been performed in this laboratory. Three major complications occurred in the first 60 studies. The first was a cerebral embolus, which developed immediately after the removal of the left heart catheters in a 49-year-old white woman who had had previous systemic emboli. The second complication was the onset of ventricular fibrillation in a 41-year-old white man. This arrhythmia developed prior to removal of the left heart catheters. Sinus rhythm was restored by cardiac massage and electric defibrillation. Both subjects had performed exercise during combined right and left heart catheterization. The complications developed approximately 15 minutes after completion of the exercise. Both patients (with mitral valve disease) died, the first 2 hours and the second 18 hours after catheterization. The third complication was in a 3[illegible]-year-old white woman with aortic stenosis. An unrecognized right hemothorax developed after the study. The patient died 8 hours later.

Because of these complications, the procedure of combined heart catheterization in this laboratory was shortened. Exercise studies are no longer planned unless the resting mitral or aortic gradient prone is of questionable significance. The only significant complication in the last 60 studies has been 1 case of hemothorax, readily treated by thoracentesis alone. In the first 60 cases, the needles employed for left atrial puncture were deliberately blunted. The needles employed in the more recent procedures have had sharp edges. Left atrial puncture has been greatly facilitated by this change in technic.

Summary

Left and combined right and left heart catheterization have greatly extended understanding of the pathophysiology of mitral valve disease. Previous concepts developed with right heart catheterization alone have proved to be limited in scope and viewpoint. The data of individual cases have been presented and discussed to elucidate some of these concepts. A classification of patients with pure mitral stenosis has been outlined, especially in relation to surgical intervention.

Acknowledgment

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Summario in Interlingua

Catheterismo cardiac sinistre e dextero-inistre in combination ha grandemente exten-ite nostre comprension del patho-physiologia e morbo del valvula mitral. Conceptiones isveloppate in le passato super le base de atheterismo dextero-cardiac sol se ha reve-te como restringite in applicabilitate e per-pectiva. Es presentate datos ab casos indi-idual, con discussiones visante a elucidar ertes de ille conceptiones. Es delineate un lassification de patientes con pur stenosis itral, specialmente con respecto al problema el intervention chirurgic.

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Kinetocardiographic Findings of Myocardial Infarction

By Soon Kyu Suh, M.D., and E. E. Eddleman, Jr., M.D.

A study of the precordial pulsations (kinetocardiograms) in patients with acute myocardial infarctions is presented. A paradoxic pulsation (bulge) over either the precordium or the epigastric area was noted in all patients studied.

ABNORMAL PULSATIONS of the chest wall due to myocardial aneurysms have been previously described [1-4] and emphasized by Dressler and Pfeiffer[5] and Vakil.[6] However, these pulsations have not been systematically evaluated by objective methods. In addition, it is not certain whether such pulsations are due to actual anatomic aneurysms or "functional" bulging of the ventricular wall. The fact that the heart may have paradoxic pulsations in myocardial infarction has been well established.[7-11] This communication presents a study of graphically recorded precordial movements (kinetocardiograms) from patients with myocardial infarctions.

Patients

Forty-two male patients with clinically and electrocardiographically proved myocardial infarctions were studied. Their ages varied from 30 to 71 years, with an average age of 51. Of the 23 patients with anterior infarctions* the lesion was acute in 17, old in 3, and of uncertain age in 3. The posterior infarctions were acute in 12 and old in 7. The 10 patients with old infarctions (including anterior as well as posterior) had clinical pictures on hospital admission suggestive of a recent lesion that could not be substantiated by serial electrocardiograms or serum transaminase levels.

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*Anterior, anteroseptal, anterior lateral infarctions were grouped together, since no significant differences were encountered in the kinetocardiograms.

Technics

Kinetocardiograms (low-frequency displacement precordial movements) were recorded with the technic previously described.[12] However, the crossbar was modified so that it could be attached directly to the bed. Thus records could be readily obtained without discomfort to the patient. Tracings were secured from positions over the precordium corresponding to the standard electrocardiographic V leads and designated as K_{3R}, K_1, K_2, etc. Tracings from other areas were labeled with a second numeral to indicate the intercostal space. Thus, K_{13} represents the record from the right parasternal position in the third intercostal space, and K_{35} the tracing from the V_3 position in the fifth intercostal space, etc. Records from points just inferior to the costal margins in the right and left midclavicular lines and just below the xiphoid process were labeled KER, KEL, and KEM, respectively. The electrocardiogram, heart sounds, and the carotid pulse were recorded simultaneously with the kinetocardiogram with use of a Sanborn Polyviso instrument at a paper speed of 50 mm. per second. Serial tracings were obtained with the same sensitivity of the recording apparatus as on the initial examination in order to determine variations in amplitude. Nine patients were studied every other day for a week and then at weekly intervals during hospitalization. Tracings were obtained from the remaining patients at weekly intervals, since it became apparent that more frequent examinations were unnecessary.

Results

Configuration of the Abnormal Pulsations

The principal kinetocardiographic change due to myocardial infarction was an abnormal outward systolic movement* reaching a maximum amplitude (peaking) in early, mid, or late systole. The tracings were classified as

*Normally the precordium retracts or moves inward during ejection; however, in the K_1 position there is a midsystolic outward movement that rarely goes above the diastolic line.

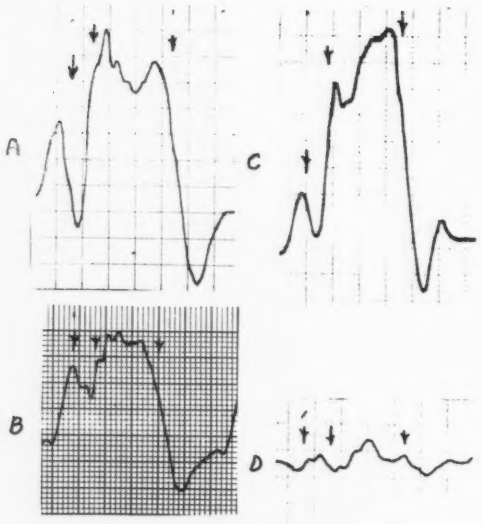

FIG. 1. The 4 types of paradoxic pulsations encountered in patients with myocardial infarctions. An upward curve on the tracing indicates an outward movement of the precordium, while a downward curve represents an inward motion. The *first arrow* indicates onset of the QRS complex of the electrocardiogram. The *second arrow* indicates the onset of ejection as determined by the carotid pulse, and the *third arrow* indicates the incisural notch in the carotid pulse. In *A*, the first type, the peak of the outward movement occurs in early systole or shortly after the onset of ejection (*second arrow*). In *B* the bulge peaks in midsystole; in *C* it peaks in late systole or just before the carotid incisural notch. Tracing *D* is a low bulge, with small amplitude; nevertheless, there is an outward systolic movement throughout the entire ejection period. The difference in *D* from *A*, *B*, and *C* is probably of no significance, as it may represent only an amplitude variation.

"high bulges" when the amplitude of the paradoxic movement was well marked, and were classified as "low bulges" when the amplitude was small. The separation of the tracings into high and low bulges is arbitrary and the differences are probably due to the many factors that can modify the absolute amplitude of precordial pulsations. These patterns are illustrated in figure 1 and the data are summarized in table 1.

A paradoxic movement of the precordium was observed in all 42 patients sometime during the 3 or 4 weeks of study. In 4 of the patients a "bulge" appeared subsequent to the initial tracing. Bulges of large amplitude (high bulges) were noted in 18 of 23 patients (78 per cent) with anterior myocardial infarctions and in 10 of 19 patients (53 per cent) with posterior infarctions. Bulges that peaked during early or late systole (fig. 1) occurred more frequently in patients with anterior myocardial infarction, whereas a prominent midsystolic movement was more common in those patients with posterior infarctions. The significance of this variation is unknown.

TABLE 1.—*The Incidence of the "Bulge" According to the Electrocardiographic Pattern*

EKG	KCG*	Early systolic	Mid-systolic	Late systolic	Total
Anterior infarction	High	8	2	8	18
	Low	2	3	0	5
Posterior infarction	High	4	6	3	13
	Low	2	4	0	6
Total		16	15	11	42

*Kinetocardiogram.

TABLE 2.—*The Location of Maximum Amplitude of the Bulges*

	Anterior infarction		Posterior infarction		
	High	Low	High	Low	Total
K_{24}	1	0	3	1	5
K_{34}, K_{33}, K_{35}	15	1	1	1	18
K_{44}	0	2	3	0	5
K_{45}	2	0	3	0	5
K_5	0	2	0	4	6
KEM	0	0	3	0	3
Total	18	5	13	6	42

Location of the Paradoxic Movements

The distribution and point of maximum amplitude of the "bulges" are illustrated in figure 2 and tabulated in table 2. The "high bulges" associated with infarctions extended from the left parasternal line to the anterior axillary line, while those associated with posterior infarctions were more frequently present in the mid, left, or right epigastric area.

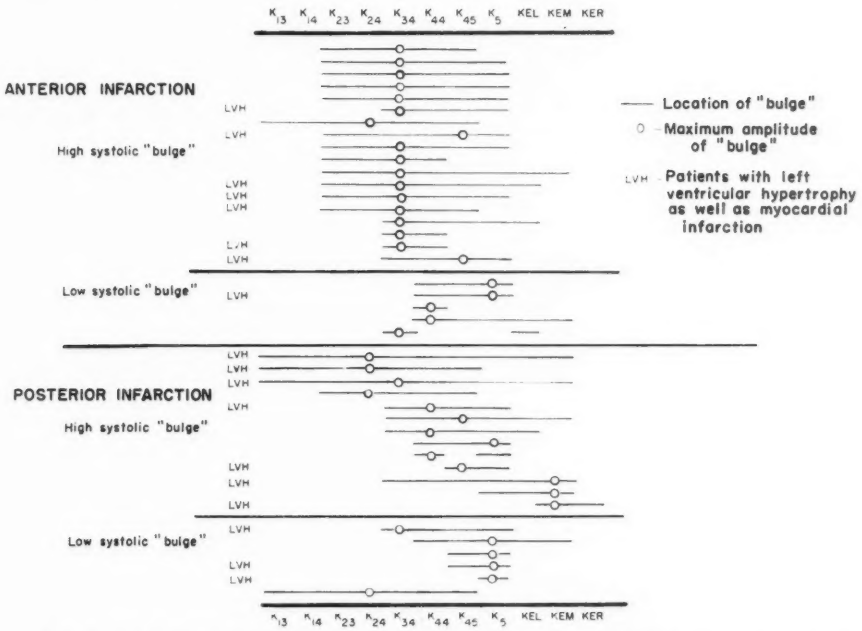

FIG. 2. The location and the maximum amplitude of the systolic bulges encountered in all of the patients with myocardial infarctions studied. K_{31}, K_1, K_3, K_4, etc., represent the points at which the kinetocardiograms were taken, the first digit referring to the "V" location and the second to the interspace. KEL refers to the left epigastrium, KEM the midepigastrium, and KER the right epigastrium. The line represents the total area where a paradoxic bulge was recorded, while the circle in the line represents the point at which the bulge was of maximum amplitude. In the anterior myocardial infarctions with high systolic bulges the maximum amplitude usually occurred at the K_{34} point, while the point of maximum bulge in the posterior myocardial infarctions was considerably more variable.

However, all patients with posterior infarctions, with 1 exception, had paradoxic pulsations over a precordium as well. The point where the bulge was of maximum amplitude in anterior infarctions was the K_3 position in 15 of the 18 patients (83 per cent) and was variable in the other 5 patients. The location of the "bulges" associated with posterior infarctions was variable. However, in contrast to anterior infarctions, only 1 patient with posterior infarction exhibited a bulge of maximum amplitude at the K_{34} point.

The upstroke of the bulges began from 0.00 to 0.18 second after the onset of the QRS complex of the electrocardiogram. The early onset at the same time as that of the QRS complex may be due to the fusion of the wave with the movements due to atrial contraction.

The Onset of the Myocardial Infarction as Related to the Kinetocardiographic Findings

Paradoxic pulsations were recorded within 5 hours after the onset of the infarction (estimated from the onset of chest pain) in 6 patients; in 1 patient, however, the "bulge" was detected 1 hour after the onset of chest pain. In contrast, in 3 of the 17 patients with acute anterior infarctions the bulge first appeared 1 week after the initial tracing.

Serial Kinetocardiographic Findings

The kinetocardiographic changes observed during the 3 weeks of hospitalization are illustrated in figure 3 and tabulated in table 3.

No changes in the serial tracings were noted in 15 patients (39 per cent). In 13 patients there were variations in amplitude or duration

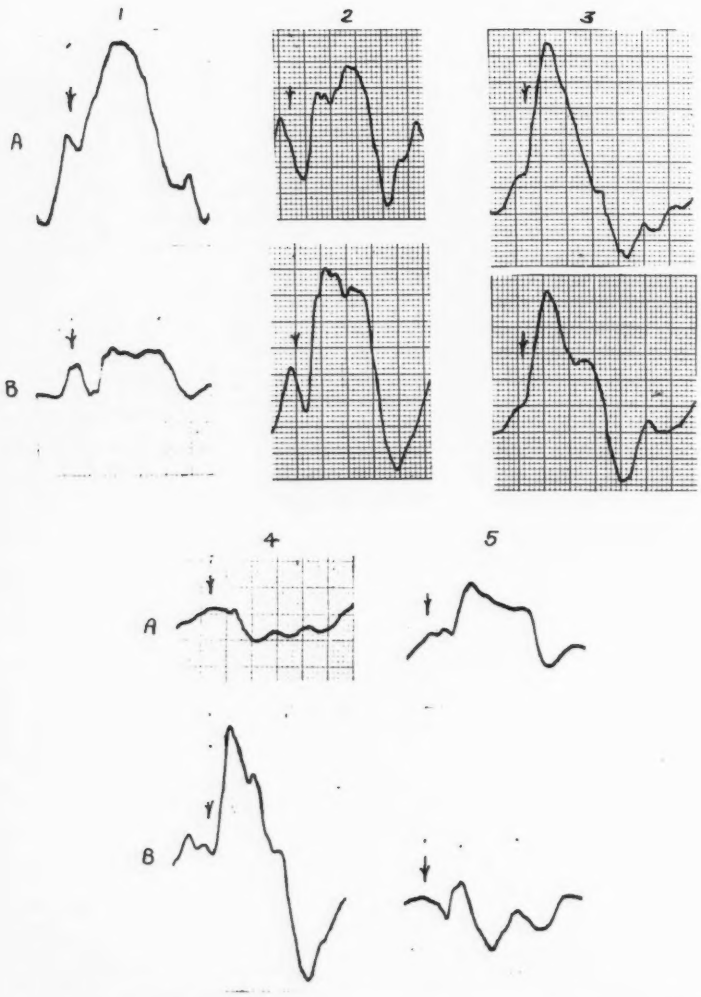

FIG. 3. The types of changes in the bulges that occurred during the 3 weeks of hospitalization. Tracing *A* represents the control record while *B* represents the change that occurred. The arrow indicates the onset of the QRS complex of the electrocardiogram. *A* and *B* under *1* represents instances in which the bulge became smaller in implitude. The tracings under *2* are those in which the bulge became greater in amplitude; *3* represents the instances in which the bulge became broader (longer duration); *4* those in which the bulge appeared during hospitalization; and *5* those in which the bulge tended to disappear with the return of the tracing toward normal.

of the bulge, and in 9 the bulge completely disappeared (22 per cent). The bulge was absent on the initial tracing in the remaining 4 patients (10 per cent) but appeared on subsequent records. Control kinetocardiograms taken prior to the infarction were available in 2 patients, and in both instances the bulge appeared only after the episode of myocardial infarction.

Findings on Palpation

In the supine position a diffuse and forceful heaving pulsation of the chest wall was pa-

TABLE 3.—*The Serial Kinetocardiographic Findings*

Location	Stage	No change	Decreased in amplitude	Increased in amplitude	Increased in duration	Developed	Disappeared	Increased then disappeared	Developed then disappeared	Total
Anterior infarction	Acute	8	3	1	0	3	2	0	0	17
	Indeterminate	0	1	0	0	0	2	0	0	3
	Old	1	0	1	0	1	0	0	0	3
Posterior infarction	Acute	3	1	0	3	0	0	3	1	11
	Old	3	3	0	0	0	1	0	0	7
Total		15	8	2	3	4	5	3	1	41

pated in 28 of the patients having large (high) kinetocardiographic bulges; however, the point of maximum pulsation was usually localized. In only 2 patients showing "low bulges" was it possible to palpate the abnormal pulsation. Thus, abnormal movements of the chest wall were palpable in 30 (71 per cent) of 42 patients, whereas the remaining 12 patients had bulges demonstrable only by the kinetocardiographic technic. Often the point of maximal pulsation was tender during the first few days of illness.

Clinical Observations

Serial changes in the kinetocardiograms were correlated with the clinical course of the patients and are tabulated in table 4.

Although 29 patients had uneventful hospitalizations, in only 6 did the abnormal bulge disappear on subsequent serial tracings. The bulge disappeared in 2 patients in whom the infarction was of an undetermined age. Of patients with old infarctions the bulge persisted in 7, appeared in 1, and disappeared in

Three of these 9 patients had anginal episodes during hospitalization with persistent systolic bulges.

There were no significant differences in the serial kinetocardiographic changes in patients with either anterior or posterior infarctions. Also there was no correlation between the kinetocardiographic changes and the laboratory findings.

The fact that the bulges often changed or even disappeared in patients with left ventricular hypertrophy indicates that the systolic outward movements were not due to left ventricular hypertrophy per se.

Kinetocardiographic and Autopsy Findings

Autopsy findings were available in 4 patients in whom kinetocardiographic traces were taken.

Patient 1. The patient was a 53-year-old man who had a typical clinical history with electrocardiographic changes of an acute anterior myocardial infarction. The patient died on the thirty-sixth day of hospitalization as the result of intractable left-sided congestive heart failure. The patient had a history of hypertension but there was no evidence of valvular heart disease. At autopsy the heart weighed 710 Gm. and both ventricular chambers were markedly dilated. There was a large mural thrombus in the apex and anterior wall of the left ventricle, next to the interventricular septum, underlying very thin myocardial muscle. Somewhat laterally and posteriorly on the left ventricle near the left atrium was a large patch of fibrinous material measuring approximately 6 cm. in diameter, which suggested an additional infarcted area. No definite myocardial aneurysm was noted. The infarcted areas appeared to be of fairly recent occurrence. Cross sections of the left coronary artery revealed complete occlusion of the left anterior descending branch approximately 2 cm. distal to the bifurcation.

Kinetocardiograms from this patient revealed a bulge with prominent early systolic

TABLE 4.—*Clinical Course and Kinetocardiographic Changes*

Stage of infarction by EKG	Clinical course and EKG changes	Systolic bulge								
		No change	Decreased in amplitude	Increased in amplitude	Increased in duration	Developed	Disappeared	Increased then disappeared	Developed then disappeared	Total
Acute	Favorable course	11	3	0	2	0	2	1	0	19
	Persisting ST elevation	0	1	0	0	0	0	0	0	1
	Angina pectoris after infarction	0	0	1	1	1	0	2	1	6
	Death due to acute left ventricular failure	0	0	0	0	2	0	0	0	2
Intermediate	Favorable course without EKG changes	1	1	0	0	0	2	0	0	4
Old	Favorable course	1	2	1	0	1	1	0	0	6
	Angina pectoris after infarction	2	1	0	0	0	0	0	0	3

Out of 4 autopsy cases, 1 patient died after the first kinetocardiographic examination and is not included in the above data. One other patient, who had a favorable course during the first 4 weeks of hospitalization, is included above under "favorable course," although he died 6 months after admission.

outward movement from K_{23} to K_{45} with maximum amplitude at K_{34}. In addition, the atrial waves were accentuated (fig. 4). Thus, the kinetocardiograms revealed a bulge of the precordium overlying the area of infarction, with a paradoxic pulsation during systole, although there was no demonstrable aneurysm present at autopsy.

Patient 2. This 69-year-old man was admitted with the usual clinical history, and electrocardiograms revealed an acute anterior infarction. There was a previous history of angina pectoris and hypertension for a duration of 8 years. The patient died 6 months later during an episode of acute pulmonary edema. At autopsy the heart weighed 600 Gm. The mid and anterior portion of the interventricular septum revealed an old thick scar which extended up to the right ventricular wall. On the anterior portion of the left ventricle just adjacent to the infarcted area of the septum was a large myocardial aneurysm. There was essentially no ventricular muscle in this area, and anteriorly the aneurysm was attached to the pericardium. The aneurysm measured approximately 7.5 cm. in diameter and was coated everywhere by mural thrombus; however, it was not filled with clotted blood. Cross sections of the coronary arteries revealed old and recent thrombi, occluding the left anterior descending coronary artery. There was marked atherosclerosis of the right coronary artery with calcification and in addition it was almost occluded.

The kinetocardiogram revealed a late systolic outward movement from K_{23} to K_5 with the maximum amplitude in K_{45} (fig. 5). In this instance the paradoxic pulsation of th

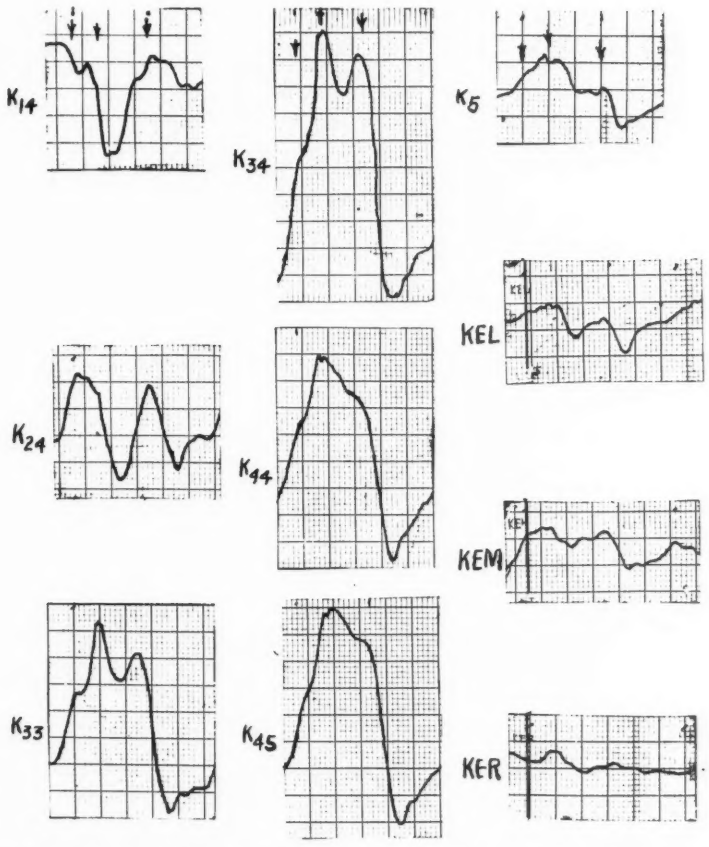

FIG. 4. Kinetocardiograms from the first autopsied patient. The tracings are aligned so that the *arrows* apply to the lower tracings as well. The area of infarction as determined at autopsy was in the region of the apex and the anterior wall of the left ventricle just adjacent to the interventricular septum. There was a marked outward systolic bulge of the anterior precordium from K_{33} to K_{45}. This represents an anterior and apical infarction in which the paradoxic systolic bulge recorded from the precordial chest wall corresponded well to the area of infarcted myocardium.

inetocardiogram occurred as the result of a rue ventricular aneurysm, and the location f the bulge recorded correlated well with the natomic aneurysm.

Patient 3. This patient was a 49-year-old ıan who had typical clinical and electrocar- iographic findings of an acute posterior myo- ırdial infarction. The patient died on the leventh hospital day following the onset of ıock and left ventricular failure. Postmortem ɛamination revealed the heart to weigh 500 m. The coronary arteries were markedly atherosclerotic, and there was a complete occlusion at a point 3 cm. from the origin of the right coronary artery. The left ventricle throughout had an extensive yellowish discoloration of its walls. There was an extensive recent infarction of the posterior wall (diaphragmatic) of the left ventricle extending up to the base of the heart.

The kinetocardiograms revealed a typical high systolic outward movement in the epigastric tracings (KEM and KER) (fig. 6). This illustrates an instance when a posterior

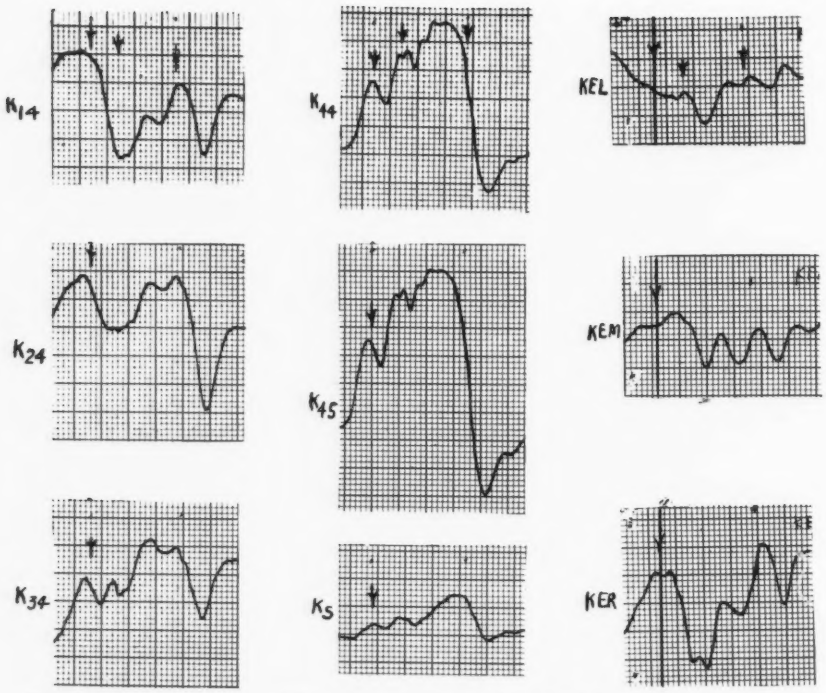

FIG. 5. Kinetocardiogram taken prior to death from the second autopsied patient. This represents an instance of a true myocardial aneurysm in the lower anterior region of the left ventricle adjacent to the interventricular septum. The kinetocardiogram revealed a systolic bulge in the areas K_{24}, K_{34}, K_{44}, and K_5. This is an example of a paradoxic precordial bulge due to an underlying anatomic aneurysm.

infarction produced paradoxic pulsations in the epigastrium. In addition this probably represents a bulge that is functional and not anatomic, as there was no demonstrable aneurysm of the myocardium at autopsy.

Patient 4. This patient was a 61-year-old man. One month prior to admission the patient had an anterior myocardial infarction. Frequent episodes of angina pectoris prompted the admission. One week later the patient had a sudden onset of very severe chest pain; just before death the electrocardiogram revealed an acute posterior myocardial infarction. The patient died a few hours later in acute pulmonary edema. At autopsy the heart weighed 470 Gm. The posterior two thirds of the septum was softened and yellowish in color. In addition, there was a patchy softening and yellowish discoloration of the subendocardial aspect of the posterior wall of the left ventricle. Both old and recent myocardial infarctions were present. The coronary arteries were sclerotic, and there was considerable narrowing of all arteries. The right coronary artery at the point where it curves over the base of the ventricle was completely occluded by hemorrhage within an atheromatous plaque. The left descending coronary artery and the left circumflex artery were sclerotic but there were no occlusions.

Kinetocardiograms did not reveal any definite bulge in the tracings taken prior to the onset of the severe pain, but the kinetocardiograms 1 week prior to death revealed an increased systolic outward movement in the KEL area and a new bulge at the K_{34} point. However, at this time there were no electrocardiographic changes (fig. 7). This patient possibly illustrates an example in which the "bulge" developed before electrocardiogra-

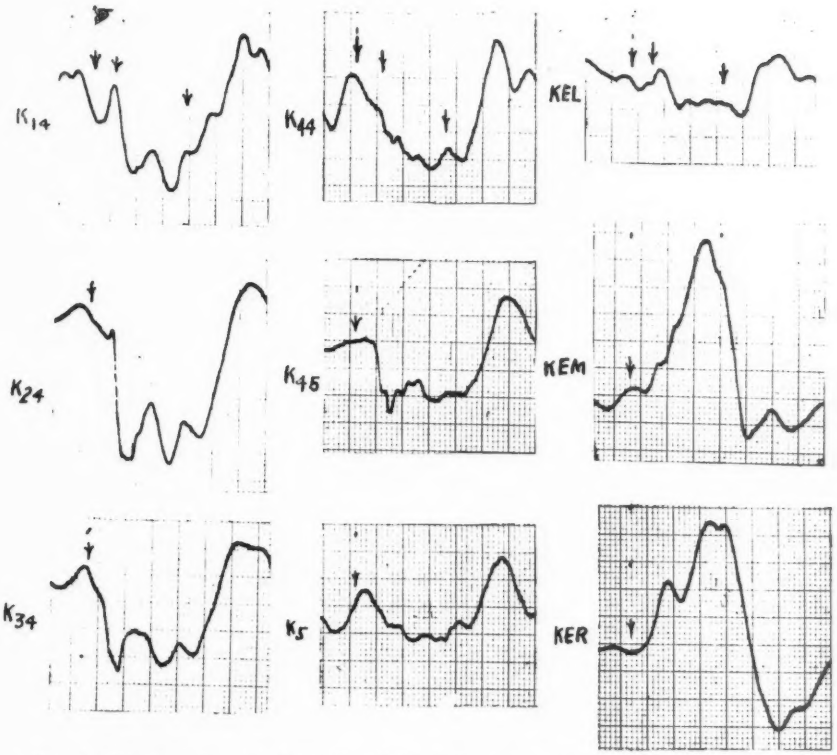

FIG. 6. Kinetocardiogram from the third autopsied patient. The myocardial infarction was in the posterior or diaphragmatic surface of the left ventricle. The kinetocardiograms in this instance revealed a marked systolic outward bulge in the right and midepigastric areas. Thus it is possible to record paradoxic pulsations in the epigastric areas in posterior or diaphragmatic myocardial infarctions.

ic changes became manifested. In addition, the finding of a bulge of the precordium with no demonstrable anterior infarction indicates that septal infarctions may produce a paradoxic pulsation of the precordium, possibly due to the bulging of the septum anteriorly into the right ventricle.

DISCUSSION

The similarity of the previously described palpable precordial pulsations due to myocardial infarctions[5, 6] to those recorded in the present study is impressive. It emphasizes the accuracy of careful clinical observations and confirms the validity of these studies.

There has been little doubt of the existence of ventricular aneurysms. There are numerous pathologic reports, and in addition systolic paradoxic bulging of the myocardium has been experimentally demonstrated by the ligation of the descending branch of the coronary artery.[13] The incidence of true aneurysms due to myocardial infarction had been reported from 9 per cent[14] to 38 per cent[3]; however, paradoxic pulsations have been noted to occur in 74 per cent of patients with recent myocardial infarctions and in 75 per cent of patients with old myocardial infarctions, as studied by the roentgenokymograph.[8] The demonstration that 100 per cent of the patients in our series had precordial or epigastric bulges was unexpected. It was anticipated that anterior infarctions would be more easily detected by the kinetocardiographic technic, whereas posterior infarctions might be better recorded with the electrokymograph

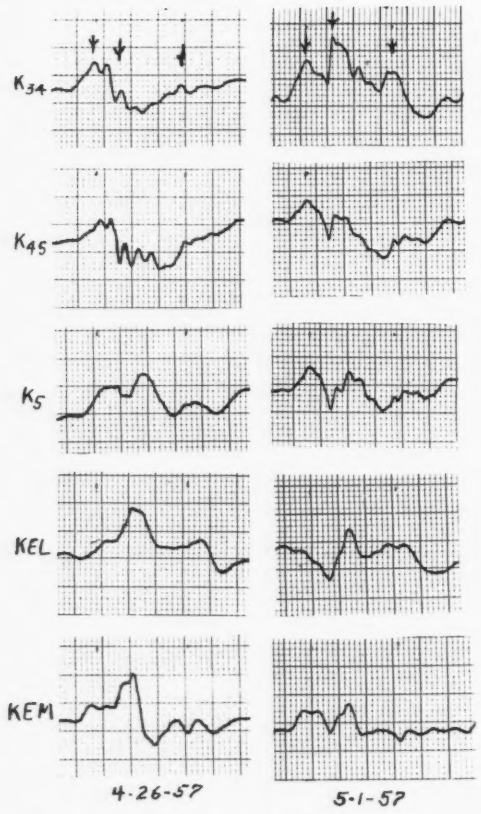

FIG. 7. Kinetocardiograms from the fourth autopsied patient were obtained before and after the development of a new myocardial infarction. In the K_{34} and K_{45} areas (control tracing) there was no outward movement during systole. However, after the infarction there occurred a well defined bulge in these areas, although the infarction in this instance was in the posterior two thirds of the septum. A possible explanation for the occurrence of an anterior precordial bulge in the presence of a septal infarction would be that the septum bulges into the right ventricle, displacing the anterior portion of the myocardium forward. This patient also probably illustrates an instance in which the bulge developed before electrocardiographic changes became manifest.

or roentgenokymograph. The fact that posterior infarctions were as frequently recorded with this technic as anterior infarctions can possibly be explained in part by the locations of the infarcts. Anatomically myocardial infarctions do not correspond very well with the electrocardiographic areas. The interventricular septum may be involved in anterior as well as posterior infarctions. The diaphragmatic area of the left ventricle is more commonly involved in posterior infarctions, and, since the epigastric area faces the diaphragmatic surface of the heart, abnormal pulsations should have been detected in this area. As the apex may be involved in posterior infarctions in addition to the septum, paradoxic pulsations obviously should be detected anteriorly. However, the only apparent explanation for the paradoxic pulsations of the parasternal areas of the chest in posterior myocardial infarctions is that the involved septum bulges into the right ventricle. High posterior infarctions are difficult to recognize electrocardiographically and none was encountered in the present series.* It would seem, however, that high posterior wall infarctions should be as silent kinetocardiographically as electrocardiographically; however, this remains to be proved.

Although it is generally accepted that an infarcted area of myocardial muscle will show a paradoxic pulsation during systole, the present study emphasizes the validity of this concept. Three of the 4 subjects in whom autopsies were performed did not have an anatomic aneurysm present, although there were demonstrable paradoxic pulsations on the kinetocardiograms. The kinetocardiogram does not differentiate between anatomic and "functional" aneurysms, except in those instances in which the bulge disappeared during observation. These therefore can be assumed to be "functional" rather than anatomic. The clinical significance of myocardial aneurysms and "functional" myocardial aneurysms remains obscure. It has been stated that the presence of a myocardial aneurysm does not alter the clinical course,[15] although instances associated with intractable heart failure have been noted. Since this was an acute study, no statement could be made as to the eventual prognosis, although only 22 per cent of the paradoxic pulsations disappeared during hos-

*It is possible that some patients were excluded who had high posterior infarctions, since only those proved by electrocardiogram or serum transaminase levels were included in this study.

pitalization. It is tempting to postulate that these 22 per cent had some recovery of muscular function to account for the disappearance of the paradoxic pulsations, and therefore one would think that they might fair better clinically. Paradoxic pulsations can be noted very early after clinical onset of the infarction, as one was recorded 1 hour after the onset of pain.

As only proved myocardial infarctions were studied in the present series, the value of this technic for diagnosis is still unknown, and whether it will be superior or comparable to the electrocardiogram is similarly unknown. However, instances were encountered in which a bulge was detected before electrocardiographic changes occurred. Previously it has been reported from this laboratory that paradoxic pulsations can occur during attacks of angina pectoris, and then disappear after the alleviation of the pain.[16] Therefore it would appear that this technic should be useful in differentiating status anginosus (coronary insufficiency) from myocardial infarctions. Any bulge present after the cessation of pain would suggest a persistent infarcted area of myocardial muscle. That the bulge did not disappear during hospitalization in 78 per cent of the patients and that no bulge disappeared within the first week of observation suggest that a persistent bulge indicates an infarction, although the age of the infarct cannot be determined kinetocardiographically. A bulge also may be present at rest in some patients with angina pectoris.[17] Whether the bulge in these instances is due to an old myocardial infarction or a chronically ischemic area of muscle is unknown.

The value of precordial palpation in the clinical examination of the patient must be emphasized again. When a paradoxic pulsation can be felt in as many as 71 per cent of the infarctions, its clinical value is obviously important. With some practice the diagnosis of myocardial infarction can often be made at the bedside or at least suspected in many instances without the electrocardiogram. In addition, the observation that the bulges were often tender to palpation is of interest. This appears to be a valid finding and not related to psychogenic factors, as the tender point always occurred at the place of the maximum bulge and not in the surrounding areas, such as on the adjacent ribs. However, the tenderness lasted only during the very acute phase of the infarction.

There are some possible difficulties in evaluating paradoxic pulsations by palpation. The apical thrust due to the presence of left ventricular hypertrophy may simulate a bulge, as the thrust is usually a very forceful outward movement, and sustained throughout systole. However, the apex impulse of left ventricular hypertrophy is usually localized in only 1 intercostal space, and usually outside the V_4 position, whereas the paradoxic bulges in myocardial infarction usually occur over most of the precordium, with the maximum impulse more frequently occurring at the V_3 area, or well inside the midclavicular line. Although the bulge due to an infarction usually has a point of maximum impulse, in general it is more diffuse in its location. However, if the infarct is confined only to the apical area of the heart, it is quite possible that clinical differentiation cannot be made. Occasionally the bulges due to myocardial infarction may be so diffusely located and so forceful that they may be confused with the anterior precordial "heave" associated with right ventricular hypertrophy. In this instance other clinical information usually offers sufficient evidence for differentiation.

Summary

Forty-two patients with clinically proved myocardial infarctions were studied with the kinetocardiographic technic (low-frequency precordial motions).

Aneurysmal bulges (paradoxic outward motions) were recorded in all patients either over the precordium or in the epigastric region, including both posterior and anterior myocardial infarctions. The point of maximum bulge was usually at the V_3 area in anterior myocardial infarctions.

Serial studies of the patients with acute myocardial infarction revealed that the bulge persisted throughout hospitalization in 78 per cent of the patients, including the 10 per cent

who had no bulge on first examination but who showed bulges on subsequent records. In only 22 per cent of the patients did the bulge disappear during the period of hospitalization.

The abnormal paradoxic pulsations were palpable in 71 per cent of the patients studied.

Autopsy findings from 4 patients revealed that the abnormal paradoxic pulsation of the chest wall corresponded anatomically rather well to the location of the myocardial infarction and could have occurred either as the result of a definite myocardial aneurysm or of paradoxic pulsations of the myocardium without definite anatomic aneurysm.

Summario in Interlingua

Quaranta-duo patientes con clinicamente demonstrate infarcimento myocardial esseva studiate per medio del technica cinetocardiographic (motiones precordial a basse frequentia).

Extrusiones aneurysmal (paradoxe motiones extrorse) esseva registrate in omne patientes—supra le precordio o in le region epigastric, in posterior e etiam anterior infarcimento myocardial. Le puncto del extrusion maximal esseva usualmente al area de V_3 in anterior infarcimento myocardial.

Studios serial del patientes con acute infarcimento myocardial revelava que le extrusion persisteva durante le integre periodo de hospitalisation in 78 pro cento del casos. Iste cifra include le 10 pro cento del patientes in qui le extrusion non esseva presente in le prime registration sed appareva in registrationes subsequente. Le extrusion dispareva in le curso del hospitalisation in solmente 22 pro cento del patientes.

Le anormal pulsationes paradoxe esseva palpabile in 71 pro cento del patientes studiate.

Constatationes necroptic in quatro casos revelava que le anormal pulsationes paradoxe in le pariete thoracic correspondeva anatomicamente satis ben al sito del infarcimento myocardial. Los occurrentia pote esser explicate como resultato de un definite aneurysmo myocardial o de pulsationes paradoxe del myocardio sin definite aneurysmo anatomic.

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Exertional Hypotension in Cardiac Patients

By Robert A. Bruce, M.D., Leonard A. Cobb, M.D., Shigeaki Katsura, M.D., John H. Morledge, M.D., W. Wyman Andrus, M.D., and Theodore J. Fuller, M.D.

Hemodynamic studies during steady states of sitting and walking on a treadmill have shown a fall in mean arterial pressure in 10 of 16 cardiac patients. This was associated with a greater increase in peripheral resistance during sitting, and a failure to increase stroke index during walking. Cardiac index during exercise increased somewhat, largely because of greater acceleration of heart rate.

IN CONTRAST to the expected rise in systolic pressure with exercise, in a previous study,[1] hypotensive responses were often recorded in 168 cardiac patients who were submitted to a test of exercise tolerance. Under the circumstances of the test, which required walking on a treadmill at 1.7 m.p.h. up a 10 per cent grade, normal subjects increased systolic pressure by a least 10 per cent of the pressure recorded during the fourth minute of sitting before standing and walking. Consequently "exertional hypotension" was defined as a failure to increase systolic pressure during walking by at least 10 per cent of the final value while sitting at rest; in some instances during exercise the pressure fell below the resting level. Forty-four per cent of patients with stenosis of either the mitral or aortic valves had exertional hypotension, as did 22 to 28 per cent of patients with either hypertensive vascular disease or coarctation of the aorta. The incidence was lower in patients who had flow loads due to either valvular regurgitation or to left-to-right shunts.

In reviewing previous experimental studies, Skouby pointed out that direct recordings of arterial pressure in horses and dogs during work on a treadmill sometimes showed a fall in mean pressure.[2] Skouby studied direct recordings of aortic pressure in dogs as they ran on a treadmill. Despite initial oscillations and transient falls of 10 mm. for less than 10 seconds, both systolic and diastolic pressures increased in parallel with the rise in oxygen consumption. Holmgren[3] also observed oscillations in pressure in human subjects during the initial phase of exercise, which he attributed to effects of immediate vasodilatation and decreased ventricular blood volume. Fraser and Chapman[4] observed in normal subjects an average rise in systolic pressure of 15 mm. Hg, an average fall in diastolic pressure of 7 mm. Hg, and no change in mean systemic pressure when arterial pressures were recorded directly during standing and during walking on a treadmill at 3 m.p.h. up a 5-per-cent grade. The same authors reported that 1 out of 9 patients with a healed myocardial infarction had a fall in mean arterial pressure during the same work load.[5] Donald and associates also noted a fall in systolic pressure in 1 out of 16 patients with mitral valve disease who were studied while they performed leg exercises in the supine position.[6] In both of these instances, cardiac index increased somewhat during exercise.

Because of the paucity of directly recorded hemodynamic data on cardiac patients during exercises in the upright posture, further studies were made to determine the mechanisms of exertional hypotension.

Material and Methods

Twenty-six patients were studied, of which 16 were placed in group I because they either exhibited no change or showed an increase in mean arterial pressure during exertion; 10 were placed in group II because they demonstrated a decrease in mean arterial pressure during exertion. The clinical and physical characteristics of these 2 groups are presented in table 1. An additional

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TABLE 1.—*Physical Characteristics, Cardiovascular Diagnosis, Preliminary Evaluation of Exercise Tolerance and Blood Volume*

									Exercise tolerance							
	Group Patients	Age	Sex	Wgt. (Kg.)	Surf. area, M.²	Cardiac diagnosis	Rhythm	Functional capacity	ECG	Symptoms	Max. sys. pres.	Max. HR	PFI	Bl. vol. (ml./Kg.)	Sedation for cardiac catheterization
I	R.D.	61	M	73.5	1.88	HMI	NS	II	2+	O	30	140	20.0	77	+
	V.W.	41	M			HCVD	NS							—	
	B.W.	36	M	65.6	1.78	AS (Post op)	NS	III	3+	ST T	54	135	7	80	+
	A.L.	47	F	59.0	1.70	HCVD	NS	III	2+	T	30	88	†4.2	74	+
	K.S.	30	F	51.8	1.52	MS	NS	III	1+	ST	20	146	8.3	62	
	K.E.	29	F	57.3		AR	NS	II	2+		42	175	10.7	57	
	A.S.	51	M	80.5	1.96	MR	NS	II	4+	VPS	10	138	†2.6	—	
	J.S.	45	M	84.0	2.05	HMI	NS	I	0	T↑	36	99	26.2	63	
	W.H.	16	M	56.0	1.65	AR	NS	II	0	—	15	116	14.3	58	+
	T.L.	47	M	105.0	2.20	HMI	NS	II	0	—	12	100	16.1	40	+
	F.C.	57	M	66.4	1.77	MS	NS	II	0	—	32	114	8.1	72	
	V.L.	23	M	89.1	2.11	AS	NS	I*	0	—	30	117	23.2	66	
	H.E.	39	F	58.7	1.68	MR	AF	III	3+	—	35	124	9.6	55	+
	E.He.	22	M	77.0	1.85	HCVD	NS	I*	0	T↑	35	100	22.0	70	
	M.F.	34	F	59.0	1.65	MS, R	NS	II	1+	—	24	115	17.6	67	+
	M.E.	30	F	60.6	1.66	MS	NS	II	3+	—	20	108	19.2	63	+
Mean		38.6		70.3							30	120	13.9	64.6±10.2	
II	A.C.	52	F	55.0	1.60	MS	AF	II	1+	ST VPS	6	138	10.7	75	
	M.H.	61	F	62.0	1.55	AR, S	NS	III	1+	—	50	94	27.4	46	+
	W.R.	32	M	85.9	2.08	AS, R	NS	I	0	—	35	115	18.1	57	
	M.G.	30	F	42.3	1.38	MR, S	NS	II	2+	—	15	180	2.5	71	
	G.G.	22	F	60.9	1.72	MR	AF	III	0	ST T↑	10	202	10.3	71	
	L.M.	52	F	65.0	1.73	HCVD	NS	III	4+	—	—30	106	12.2	59	+
	J.R.	46	M	66.2	1.81	MS, R	NS	III	4+	ST	—16	140	8.2	52	+
	H.G.	30	F	57.7	1.63	MS	NS	III	3+		— 2	167	3.3	—	
	G.R.	36	F	61.0	1.65	MS	AF	II	4+		—10	200		—	
	E.H.	61	M	85.0	1.97	HMI	NS	II	2+	VPS	36	115	16.0	52	+
Mean		42.2		64.1	1.71						9.4	146		60.4±10.6	

*Not digitalized.

†Poor motivation.

HMI, healed myocardial infarction; HCVD, hypertensive cardiovascular disease; AS, aortic stenosis; MS, mitral stenosis; AR, aortic regurgitation; MR, mitral regurgitation; NS, normal sinus rhythm; AF, atrial fibrillation; Max. HR, maximal heart rate; PFI, physical fitness index.

5 patients who were sedated became weak or dizzy on sitting up and were eliminated from the study.

A preliminary test of exercise tolerance was done on each patient to determine blood pressure response by means of a sphygmomanometer, and to note any symptoms or signs resulting from exertion. Cardiorespiratory performance was expressed in terms of the Physical Fitness Index.[7]

Thirteen patients were sedated with 25 mg. of meperidine hydrochloride (Demerol), and 25 mg. of dimenhydrinate (Dramamine) in preparation for surgical exposure of the median basilic vein and the radial artery under local anesthesia with procaine. They were then given 25 mg. of ephedrine sulfate intramuscularly to prevent postural hypotension during sitting and standing as a result of previous sedation. The remaining patients received only 1 ml. of saline subcutaneously as a placebo.

A polyethylene catheter (PE 90) was inserted into the radial artery, and the venous catheter (6F) was passed into the pulmonary artery.

TABLE 2.—*Effects of Upright Posture and Exercise (Mean ± Standard Deviation and Probability of Difference between Means Being due to Chance Alone*)*

	Group†	Lying supine	Sitting	p	Walking	p
Ventilation	I	7.2±1.8	11.0±2.5	<.001	26.7±7.5	<.001
(L./min.)	II	7.9±3.0	10.0±3.1		26.6±7.8	<.001
O_2 removal rate	I	39.5±14.0	28.0±6.6	<.006	34.5±10.6	
(ml./L.)	II	34.5±12.5	28.0±7.3		30.7±13.9	
O_2 consumption index	I	151±36	164±19		487±104	<.001
(ml./min./M.^{2})	II	150±56	153±26		442± 45	<.001
Arterial O_2 content	I	17.3±2.8	18.4±2.3		18.6±2.7	
(vol. %)	II	16.9±1.9	17.9±1.6		18.2±1.6	
Mixed venous O_2 content	I	12.4±3.8	11.7±2.5		8.4±2.7	<.001
(vol. %)	II	11.3±2.1	10.7±2.0		5.8±1.7	<.001
A-V O_2 difference	I	52±10	66±14	<.001	101±27	<.001
(ml./L.)	II	56± 4	71±18		124±27	<.001
Cardiac index	I	2.95±0.59	2.56±0.58		5.05±0.46	<.001
(L./min./M.^{2})	II	2.73±0.94	2.22±0.47		3.61±0.35	<.001
Heart rate	I	71±14	83±17		112±21	<.001
	II	71±18	80±16		129±31	<.001
Stroke index	I	43±10	32±9	<.001	50±6	<.001
(ml./M.^{2})	II	40±14	29±7		30±13	
Mean pulm. press.	I	23±11	24±14		35±19	
(mm. Hg)	II	25±10	26±14		36±22	
Mean syst. press.	I	108±25	115±22		131±22	
(mm. Hg)	II	102±24	124±26		114±28	
Total pulm. resist.‡	I	65±42	75±42		65±53	
dynes sec. cm.$^{-5}$ × M.^{2}	II	80±38	107±82		95±74	
Total syst. resist.‡	I	303± 84	375± 34	<.002	228± 84	<.001
dynes sec. cm.$^{-5}$ × M.^{2}	II	325±107	463±121	<.007	276±139	<.002

*In changing from lying to sitting, or from sitting to walking, for the same group of patients.

†I, 16 patients with normal pressor response to exercise; II, 10 patients with hypotensive response to exercise.

‡Expressed as 1/10 of calculated values.

Cardiac outputs were determined by direct Fick technic during steady states of sitting and walking. Oxygen consumption was measured with a 13-liter respirometer filled with 100-per cent oxygen. Blood oxygen contents were determined by the Van Slyke-Neill method.

Blood volume was estimated from T-1824 plasma concentration, at equilibrium, 2 to 3 minutes after directly recording the primary dilution curve with an ear oximeter and logarithmic amplifier;[8] venous hematocrit was used without any correction for trapped plasma.

Blood pressures were recorded with Statham P23D transducers and a Sanborn oscillograph. Zero reference levels were located 10 cm. above the table when the patient was supine, and at the level of the fourth interspace anteriorly when the patient was upright. Transducers were taped to the arm, which was held dependent, to maintain constant positions during walking. Catheters were flushed at frequent intervals to prevent damping. No corrections were made for respiratory variations, and mean pressures of more than one respiratory cycle were determined by planimetric integration.

Pulmonary and systemic resistances were calculated from mean pressure and flow corrected for body surface areas, as follows:

$$\textit{Resistance Index (dynes sec. cm.}^{-5} \times M.^2) = \frac{\textit{Mean pressure} \times 1332 \times 60}{\textit{Cardiac index}}$$

A Valsalva maneuver, standardized by holding orotracheal air pressure at 40 mm. Hg for 10 seconds, was recorded in several patients to observe responses in systemic arterial pressure during phases II and IV.

Results

The results observed in 13 sedated and 13 nonsedated patients were combined and subdivided into 2 groups according to the pressor response to walking. Since 6 nonsedated patients developed exertional hypotension in contrast to only 4 of the sedated patients who were able to sit up, it is likely that sedation selectively eliminated several of the more vulnerable patients from complete study.* The hemodynamic effects of the upright posture and exercise will be described in relation to

*Tabulation of all individual data in a mimeographed appendix will be supplied on request.

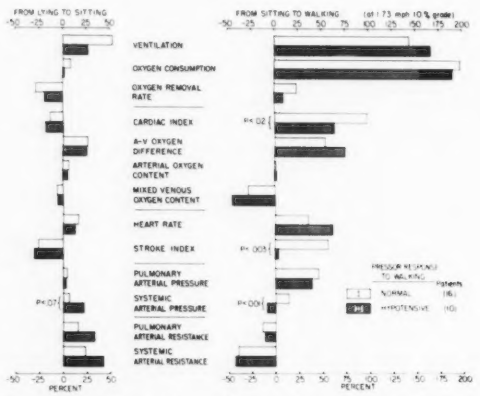

FIG. 1. Comparison of average percentage changes in 26 cardiac patients as a result of sitting upright and of walking. Patients in group I and II were separated on basis of change in mean arterial pressure from sitting to walking; note significance of changes in stroke and cardiac indices.

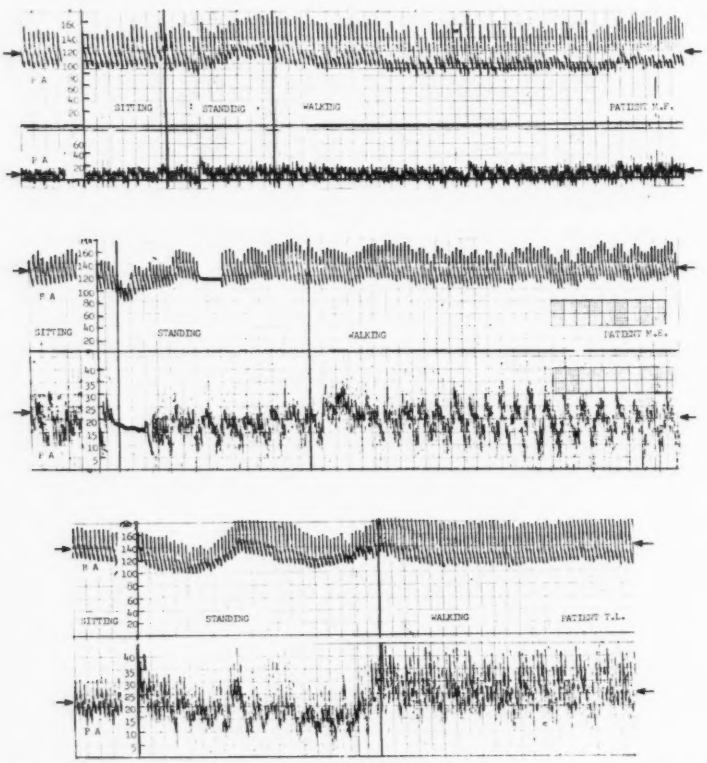

FIG. 2. Variations in arterial pressures observed during standing and walking in 3 different patients. Arrows indicate level of mean arterial pressure.

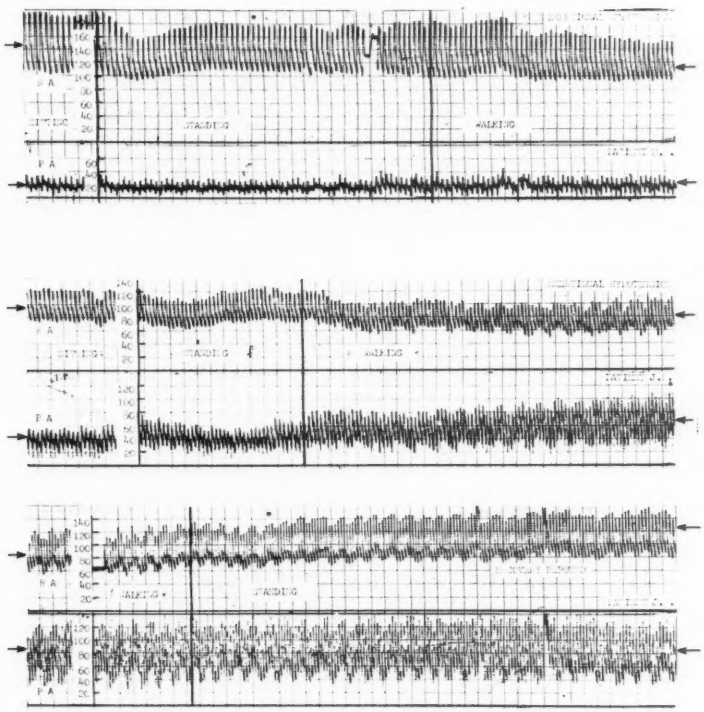

FIG. 3. Two examples of exertional hypotension (*top*, M. H.; *bottom*, J. R.). Note the fall in systolic as well as mean arterial pressure.

16 patients with a normotensive, and 10 patients (38 per cent) with a hypotensive response to exercise in the upright posture.

Effects of Sitting and Standing at Rest

Several adaptations in circulation occurred as a result of changing from the supine to a sitting position (table 2, fig. 1). Presumably, venous pooling affected venous return, widened the arteriovenous oxygen difference about 25 per cent, and lowered the cardiac index. There was a significant reduction in stroke index of more than 25 per cent, and only a slight acceleration of heart rate. Although the magnitude of increased pressure and peripheral resistance was greater in group II patients, the differences were not significant ($p < .07$ and .12 respectively).

Some patients exhibited slow oscillations, or undulations in systemic arterial pressure, when they stood up (fig. 2). These fluctuations were not well correlated with respiratory variations in pulmonary arterial pressure.

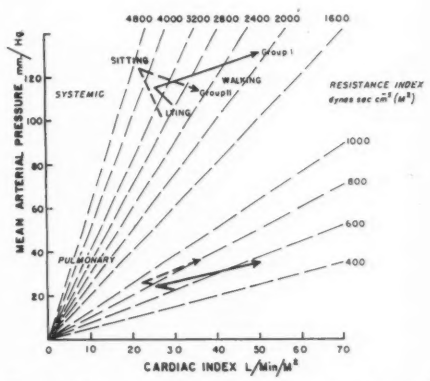

FIG. 4. Comparison of changes in average cardiac index, systemic and pulmonary arterial pressures, and total resistances as a result of sitting up and of walking.

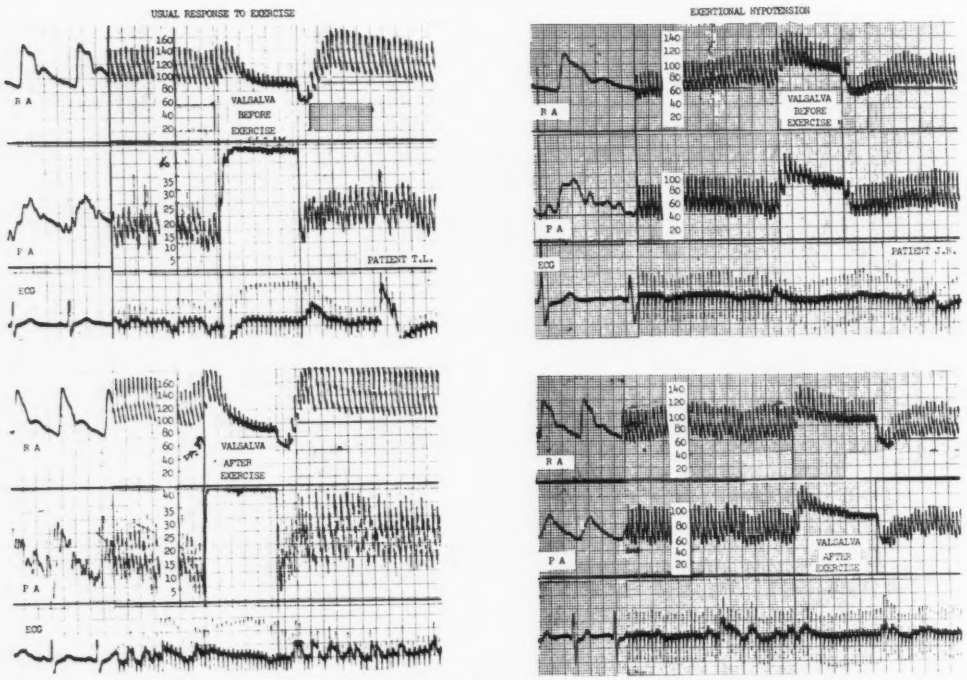

FIG. 5. Variations in phase-II responses in arterial pressure to Valsalva maneuver in 2 different patients. Note the transient increase in diastolic pressure in phase IV after the Valsalva maneuver.

Effects of Walking

For approximately a 3-fold increase in oxygen consumption above the level observed while supine, patients in group I almost doubled the cardiac index (table 2). They also showed about a 50 per cent increase in stroke index and arteriovenous oxygen difference in changing from sitting to walking (fig. 1). Since mean arterial pressure increased but slightly, the peripheral resistance showed about a 40 per cent fall due to vasodilation (fig. 3).

Patients in group II with exertional hypotension (figs. 3 and 4) showed a similar fall in resistance, but a significantly smaller increase in stroke index ($p < .003$) and cardiac index ($p < .02$) than did those in group I. The increase in arteriovenous oxygen difference was somewhat greater, but there were no appreciable differences in heart rate, oxygen consumption, ventilation, or oxygen removal rate.

Contributory Factors for Exertional Hypotension

The possible importance of abnormalities in total blood volume, distribution of blood volume (as reflected in pressor responses to the Valsalva maneuver), and mechanism of heart beat was reviewed.

There was neither a significant reduction in blood volume nor a significant difference in average total blood volume for patients in groups I and II (table 1).

Valsalva responses were recorded on 16 patients. Only the 2 hypertensive patients who were taking a sympathetic blocking agent orally showed any impairment of the post-Valsalva overshoot in diastolic pressure. There was no consistent difference in phase II responses between the 2 groups. Examples of maximal differences observed between patients in each group are shown in figure 5. Furthermore, there was no change in these responses

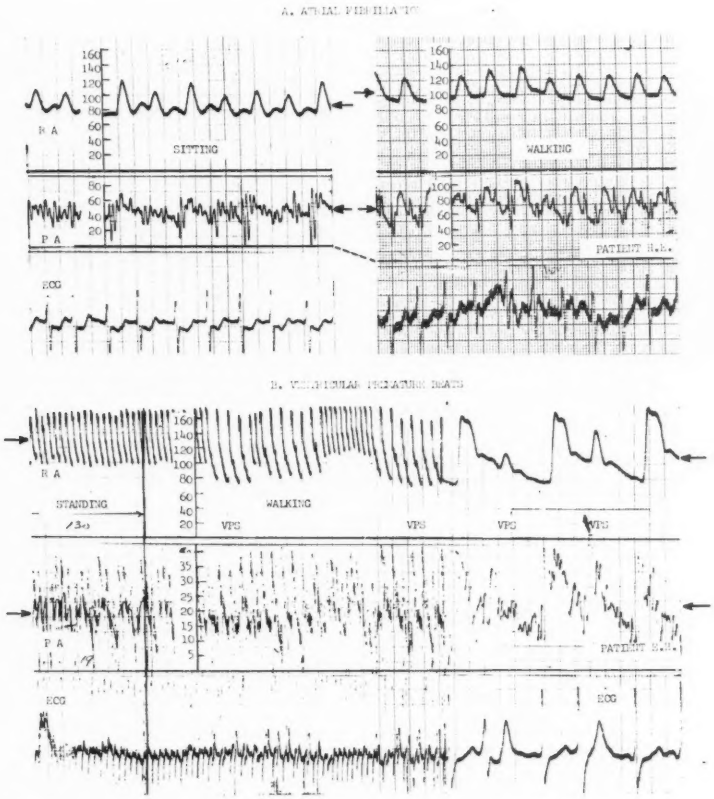

FIG. 6. Variations in arterial pressure in relation to atrial fibrillation and ventricular bigeminy in 2 patients. Note the fall in mean arterial pressure in the latter instance.

when the Valsalva maneuver was repeated after the exercise test.

Three of 4 patients who had atrial fibrillation developed exertional hypotension. The exceptional patient, who increased mean arterial pressure during exertion (fig. 6), had predominantly mitral regurgitation. The diagnostic impression was confirmed later during open heart surgery (mitral annuloplasty performed by Dr. K. Alvin Merendino). Of the 3 others with atrial fibrillation and hypotensive responses to exertion, 2 had predominantly mitral stenosis; the other had mitral regurgitation and possibly myocarditis. Another patient, E. H., had normal sinus rhythm at rest, but exhibited a fall in mean arterial pressure due to the onset of ventricular bigeminy during exertion (fig. 6). Since he had a healed myocardial infarct, and was not treated with any digitalis preparation, this arrhythmia was presumably due to myocardial ischemia.

DISCUSSION

Even though exertional hypotension has previously been observed directly in some experimental animals and indirectly in cardiac patients studied in this laboratory, the possibility of technical errors in these studies should not be disregarded without further comment. Due to the sampling of blood and flushing of catheters during the procedures, the possibility of artifactual damping is remote. Most important, however, is the fact that many patients exhibited a rebound to higher radial arterial pressures during recovery, as has been observed previously in

older normal men by Fraser and Chapman.[4]

Numerous mechanisms may contribute to a depressor response to muscular exercise. Undoubtedly neural regulation of vasomotor tone is important. This may be impaired by the syndrome of orthostatic hypotension, or by depression from the use of narcotics or sedatives.[9] The latter was presumed responsible for eliminating 5 patients from complete studies, since without sedation, they could tolerate the upright posture and exercise in the preliminary test prior to cardiac catheterization. Further support of this is the fact that all of the nonsedated patients completed the experimental procedure. An effective blockade of peripheral ganglia may impair regulation of vasomotor tone also. Although 2 hypertensive patients (A.L. and L.M.) had been on prolonged therapy with pentolinium bitartrate, one showed the hypotensive response to posture previously described by Smith and Hoobler[10] while the other showed it in response to walking. Presumably marked reductions in blood volume from hemorrhage or dehydration also could assume major importance if neural regulation of vasomotor tone was not adequate. Pulmonary hypertension may be contributory in favoring a redistribution of the effective blood volume, but this could not be evaluated adequately from the 2 examples included in this study. Hypocapnia from hyperventilation may lower peripheral resistance,[11] but the mean arterial carbon dioxide content during exercise of 43.0 volumes per cent for 4 patients with exertional hypotension was not significantly different from the mean (43.9 volumes per cent) for the other 9 patients who had lower levels of ventilation (23.1 versus 27.0 L./min.), and no fall in pressure.

Although the role of posture in relation to numerous cardiovascular syndromes has been reviewed by Silverman and Salomon, observations during physical activity in the upright posture were not available for analysis in their study.[12] The cardiac patients in the present study who exhibited a depressor response to exercise usually demonstrated a greater pressor response to changing from supine to sitting posture. This was in compensation for a somewhat greater reduction in cardiac index. The decreased peripheral resistance from vasodilatation secondary to muscular exercise in individuals in group II was comparable to that observed in other cardiac patients in group I who had a pressor response to exertion. Thus exertional hypotension was a physical sign of impaired cardiac reserve, primarily due to inability to increase the stroke index because of myocardial ischemia, dilatation, valvular stenosis, or ventricular bigeminy. Tachycardia, although it increased cardiac index, was not a sufficient compensation for this defect. In fact if tachycardia were excessive, particularly with atrial fibrillation, it would further limit stroke by the greater reduction in diastolic filling time. Valvular regurgitation, when not associated with significant cardiac dilatation, myocardial disease or depression of neural regulation of vasomotor tone, was unlikely to cause exertional hypotension. Similarly, a previous study of 13 congenital cardiac patients with left-to-right shunts and no significant myocardial disease did not demonstrate exertional hypotension.[13]

Summary and Conclusions

Exertional hypotension, or a fall in mean systemic arterial pressure during walking, occurred in 10 of 26 patients tested with indwelling catheters and direct recordings of pressure in pulmonary and radial arteries.

Patients who developed exertional hypotension had slightly increased peripheral resistance and lowered cardiac indices while sitting at rest, and a marked limitation of stroke index during walking. Cardiac index usually increased somewhat due to acceleration of heart rate.

It is concluded that exertional hypotension may be a significant manifestation of impaired cardiac function whenever a major loss in blood volume or a marked impairment of neural regulation of vasomotor tone can be excluded.

Summario in Interlingua

Hypotension de effortio, i.e. un reduction del valor medie del tension arterial systemic in ambulation, occurreva in 10 ex 26 patientes

state con catheteres in sito e registration recte del tension in arterias pulmonar e dial.

Patientes qui disveloppava hypotension de fortio habeva levemente augmentate resistentias peripheric e reducite indices cardiac quando illes sedeva in stato de reposo e un marcate limitation del indice de pulso quando illes ambulava. Le indice cardiac cresceva in general levemente in consequentia de un augmento del frequentia cardiac.

Es concludite que hypotension de effortio es possibilemente un manifestation significative de dysfunction cardiac in omne casos in que il es possibile excluder le explication per major perditas de sanguine o per marcate dysfunction del regulation neural del tono vasomotori.

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Electrocardiographic Changes during Hemodialysis with the Artificial Kidney

II. The Treatment of Digitalis Intoxication

By GLENN D. LUBASH, M.D., BURTON D. COHEN, M.D., WARREN S. BRAVEMAN, M.D., ALBERT L. RUBIN, M.D., AND E. HUGH LUCKEY, M.D.

In a series of 63 hemodialyses with the artificial kidney, digitalis had been administered 30 times. The occurrence of digitalis intoxication is discussed and the results of treatment are analyzed.

IN A PREVIOUS communication[1] we reported that hemodialysis with the artificial kidney consistently corrects acidosis, hyperpotassemia, and hypocalcemia. We have observed, as have others,[2, 3] that the patient with heart disease receiving digitalis may manifest electrocardiographic changes of "digitalis effect" and toxicity during repair of fluid and electrolyte imbalance.

The management of digitalis toxicity often includes modification of plasma electrolyte concentrations. The administration of potassium salts[3] or reduction of plasma calcium concentration by chelating agents[4, 5] is frequently successful. Clinical response and plasma electrolyte change, however, often fail to parallel each other. Therapeutic successes in the absence of demonstrable change in measurable plasma ionic constituents have been attributed to change in intracellular concentration, to altered ion gradients, or to altered rate of ion transfer at the cellular membrane.[1] Lack of clinical response, despite demonstrated elevation of plasma potassium, has also been observed. Exact mechanisms for therapeutic success or failure are poorly understood.

We have previously reported an analysis of electrocardiographic changes in 33 hemodialyses and have correlated them with plasma electrolyte concentrations.[1] Since then a larger series of patients has been observed. This report summarizes our experience with digitalis intoxication during 63 dialyses performed on 51 patients with acute and chronic renal disease. There were 25 patients with congestive heart failure in this group who were receiving maintenance doses of digitalis (digitoxin) up to the time of dialysis. They were treated with dialysis 30 times. Seven patients showed evidence of digitalis intoxication during 9 dialyses. Analysis of our data may better define the limitations of current therapy of digitalis intoxication during hemodialysis.

CRITERIA FOR DIAGNOSIS OF DIGITALIS INTOXICATION

The criteria for digitalis intoxication were limited to rigidly interpreted electrocardiographic manifestations. These included ectopic supraventricular tachycardia, atrioventricular block, or ventricular irritability occurring in a patient previously exhibiting normal sinus rhythm, in the absence of symptoms and signs of concomitant illness (pulmonary infarction, infection, etc.) that might induce or be associated with arrhythmia. Subjective manifestations of digitalis intoxication were rejected for 3 reasons. Each of these patients presented the uremic syndrome, so that anorexia, nausea, and vomiting were common without relation to medication. Secondly, antiemetics, which might have obscured such phenomena, had been administered to many patients and, finally, results could be evaluated better by objective measurements.

From the Cardio-Renal Laboratory of the Second (Cornell) Medical Division, Bellevue Hospital, the Medical Service of the New York Veterans Administration Hospital, and The New York Hospital-Cornell Medical Center, New York, N.Y.

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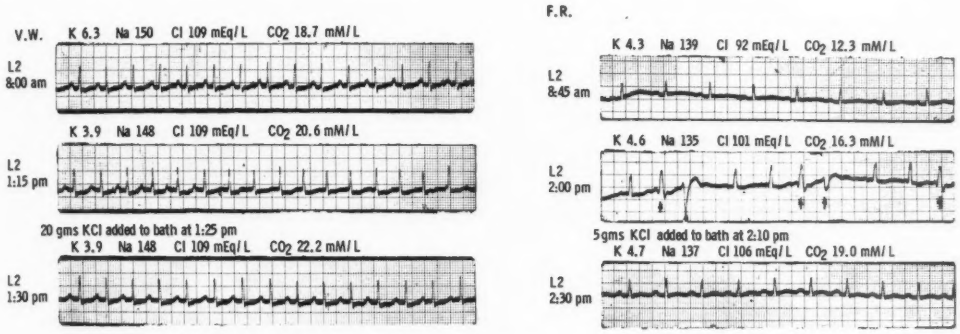

FIG. 1 *Left.* Electrocardiographic changes in case 4. A supraventricular tachycardia, probably nodal in origin, appeared at 1:15 p.m., associated with correction of hyperpotassemia. After the addition of 20 Gm. of potassium chloride to the dialysis bath at 1:25 p.m. the rhythm changed to sinus tachycardia, but the plasma potassium level was unchanged after this therapy.

FIG. 2 *Right.* Electrocardiographic changes in case 5. Frequent multifocal ventricular premature contractions occurred at 2:30 p.m. associated with the correction of acidosis. Plasma potassium had not changed significantly. After the addition of only 5 Gm. of potassium chloride to the dialysis bath at 2:10 p.m. the arrhythmia disappeared. Plasma potassium concentration did not change significantly.

Arrhythmias were uncommon in patients who had not received digitalis. Several patients had premature ventricular contractions without other arrhythmia or significant electrolyte change. Some severely ill patients developed atrial fibrillation with a rapid ventricular rate during hemodialysis. They were treated with digitalis and are not considered further in this report.

The technics employed for blood sampling and plasma analysis have been described previously.[1]

RESULTS

Digitalis intoxication was noted in 30 per cent of the dialyses of the patients receiving digitalis. In 26 patients treated by hemodialysis who had no prior digitalis therapy, there was no similar electrocardiographic change. In 2 patients whose dialysis was repeated, the signs of digitalis intoxication appeared on each occasion. Neither age nor sex seemed significant determinants. The cause of renal failure was varied and had no significant relationship to digitalis intoxication. Only 2 patients had had evidence of any cardiac alteration prior to the onset of renal failure. This consisted in the electrocardiographic pattern of left ventricular hypertrophy in each case.

In every instance the arrhythmia appeared during the correction of acidosis, hyperpotassemia, hypocalcemia, or combinations of these. The only treatment employed to correct the arrhythmia consisted in the addition of potassium chloride to the dialysis bath. Short case summaries follow. The serial electrocardiograms in cases 1, 2, and 3 have been published previously.[1]

Case 1. E. K., a 16-year-old girl suffering from chronic pyelonephritis, developed nodal rhythm during dialysis. Plasma potassium concentration which was 7.4 mEq./L. initially measured 4.7 mEq./L. at the onset of arrhythmia. Carbon dioxide combining power had risen from 10.8 to 17.2 mM/L. Thirty grams of potassium chloride were added to the dialysis bath and the rhythm soon changed to sinus tachycardia. At that time, plasma potassium concentration was 4.8 mEq./L.

Case 2. C. O., a 10-year-old girl with acute nephritis, developed nodal rhythm or atrioventricular dissociation during dialysis. Plasma potassium concentration was 7.4 mEq./L. initially and 4.0 mEq./L. at the onset of arrhythmia. Carbon dioxide combining power had risen from 8.4 to 18.8 mM/L. Twenty grams of potassium chloride were added to the dialysis bath, and the rhythm was converted to normal sinus mechanism. Plasma

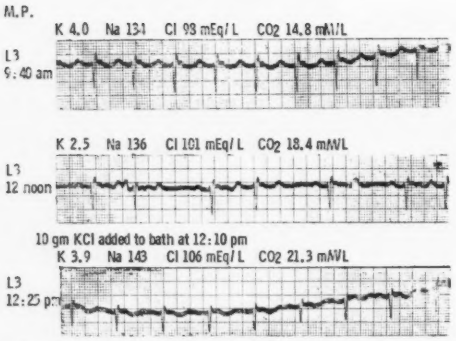

FIG. 3. Electrocardiographic changes in case 7. At 9:40 a.m. the rhythm was normal sinus. (The slur on the downstroke of the r' was also present on the electrocardiogram at 12 noon and does not indicate the presence of atrial flutter.) At 12 noon first- and second-degree heart block were noted in association with hypopotassemia and slight correction of acidosis. After the addition of 10 Gm. of potassium chloride to the dialysis bath at 12:10 p.m. the arrhythmia was no longer present.

potassium concentration at that time was 3.9 mEq./L.

During a second dialysis, paroxysmal atrial tachycardia with block was noted. Before this event plasma potassium concentration had changed from 7.4 to 3.6 mEq./L. and carbon dioxide combining power from 11.7 to 21.8 mM/L. After addition of 30 Gm. of potassium chloride to the dialysis bath, the plasma potassium was 4.1 mEq./L. and the rhythm was sinus tachycardia.

Case 3. R. F., a 42-year-old man considered to have subacute glomerulonephritis, manifested the electrocardiographic pattern of left ventricular hypertrophy. He developed premature ventricular contractions giving rise to quadrigeminy during dialysis. Subsequently he exhibited paroxysmal atrial tachycardia with block. During these intervals the serum calcium concentration had risen from 7.4 to 9.5 mg. per cent. There was no significant change in plasma concentrations of potassium or bicarbonate. No therapy was instituted and in a short period of time the rhythm changed to sinus tachycardia.

Case 4. V. W., a 43-year-old man with extensive burns and acute renal failure, developed a supraventricular tachycardia, probably nodal in origin, during dialysis. Plasma potassium concentration, initially 6.3 mEq./L., was 3.9 mEq./L. at this time. Twenty grams of potassium chloride were added to the dialysis bath and the rhythm changed to sinus tachycardia. The plasma potassium was unchanged at a concentration of 3.9 mEq./L. (fig. 1).

Case 5. F. R., a 52-year-old woman with chronic glomerulonephritis, developed multifocal premature ventricular contractions during hemodialysis. Carbon dioxide combining power, which had been 12.3 mM/L. at the start of dialysis, was 16.3 mM/L. Plasma potassium concentration remained normal. Only 5 Gm. of potassium chloride were added to the dialysis bath and the premature ventricular contractions disappeared (fig. 2).

Case 6. J. R., a 57-year-old man with acute renal failure, was treated with hemodialysis on 2 occasions. The electrocardiographic pattern of left ventricular hypertrophy was present. During the initial dialysis, first-degree heart block was noted concomitant with reduction in plasma potassium from 5.5 to 3.4 mEq./L. and an elevation of carbon dioxide combining power from 22.2 to 27.5 mM/L. No treatment was directed toward the first-degree heart block, which persisted for 12 hours after completion of dialysis. During the second dialysis, first-degree heart block again appeared as plasma potassium changed from 5.1 to 3.9 mEq./L. On this occasion, 30 Gm. of potassium chloride were added to the dialysis bath and plasma potassium concentration rose to 4.8 mEq./L. First-degree heart block persisted, however, until after dialysis.

Case 7. M. P., a 52-year-old woman with chronic pyelonephritis, developed first- and second-degree heart block during dialysis. Plasma potassium had changed from 4.0 to 2.5 mEq./L. Ten grams of potassium chloride were added to the dialysis bath and plasma potassium rose to 3.9 mEq./L. Concurrently, the heart block disappeared (fig. 3).

DISCUSSION

In all 9 instances in which the manifestations of digitalis intoxication occurred they were relatively benign, and idioventricular rhythm was not observed, suggesting that these more serious manifestations of digitalis intoxication are relatively rare during hemodialysis.

The management of digitalis-induced arrhythmias should include the addition of potassium chloride to the dialysis bath. The limitations of supplementary potassium chloride administration, however, are evident. In 6 of 9 instances, this treatment appeared effective but the plasma potassium concentration after the addition of potassium to the dialysis bath in 2 of these successful cases was the same as or lower than that at the time of toxicity. We have data to demonstrate an

teration in cellular potassium concentration uring hemodialysis,[6] and have regarded an tered intracellular extracellular potassium adient or potassium transfer rate across the llular membrane as an important mechasm in these cases. An explanation is still eking for the spontaneous reversion of the rhythmia in case 3 and for the failure of potssium chloride administration (in the face concomitant elevation of plasma potassium) case 6.

Rapid elevation of serum calcium can play an important role in the development of digitalis toxicity, since calcium and digitalis have long been known to be synergistic in action.[7] Case 3 may illustrate such mechanism.

The recent development by Wacker and Vallee[8] of an accurate method of measuring serum magnesium concentration has allowed comparison of the similarities of electrocardiographic changes produced by hyperpotassemia and by hypermagnesemia. It is possible that a reduction of serum magnesium from elevated levels during hemodialysis may contribute to the defects of rhythm and conduction of digitalis intoxication.

Digitalis intoxication constitutes a hazard to many patients undergoing hemodialysis. It is impossible to predict its occurrence, and results of treatment are occasionally unsatisfactory. It appears advisable, therefore, to defer the administration of digitalis until after hemodialysis whenever possible. A more rational approach must await further clarification of the pathogenesis of digitalis toxicity during hemodialysis. In any case, during hemodialysis, frequent electrocardiographic observations are warranted for early detection of digitalis intoxication.

Summary

The appearance and management of digitalis intoxication during 63 hemodialyses with the artificial kidney have been analyzed. Digitalis had been administered in 30 instances. In 9 instances digitalis-induced arrhythmias were observed. Their occurrence had no relation to age, sex, or cause of renal insufficiency.

In all instances the arrhythmia was relatively benign, and idioventricular rhythm was not observed. The addition of potassium chloride to the dialysis bath was effective in 6 cases, although the mechanism of action appears obscure in 2 of these. In 1 patient, treatment failed, and in another spontaneous reversion to sinus rhythm was observed.

Continuous electrocardiographic monitoring is necessary during hemodialysis. It appears advisable to avoid treatment with digitalis before the procedure whenever possible or to remain alert to the problem of induced toxicity if digitalis administration is urgent.

Acknowledgment

We wish to thank Dr. Thomas P. Almy and Dr. J. J. Smith, Directors of the Medical Services of the Second (Cornell)) Medical Division of Bellevue Hospital and the New York Veterans Administration Hospital, respectively, for their interest. We are grateful to Dr. Norton Spritz, Dr. David Brailovsky, and Dr. George Frimpter, who participated in many of the dialyses. Mrs. Ruth Aronson, Miss Carolyn Register, and Miss Naomi Schechter contributed invaluable technical assistance.

Summario in Interlingua

Le apparition e le tractamento de intoxication per digitalis in 63 hemodialyses per medio del ren artificial esseva analysate. Digitalis habeva essite administrate in 30 casos. In 9, arrhythmias inducite per digitalis esseva observate. Lor occurrentia esseva sin relation con etate, sexo, o causa del insufficientia renal.

In omne casos le arrhythmia esseva relativemente benigne. Rhythmo idioventricular non esseva observate. Le addition de chloruro de kalium al banio de dialyse esseva efficicace in 6 casos. In 2 de illos, le mechanismo del action remaneva obscur. In 1 patiente, le tractamento non succedeva. In un altere, reversion spontanee al rhythmo sinusal esseva observate.

Continue controlo electrocardiographic es necessari durante le hemodialyse. Il pare desirabile evitar tractamento a digitalis ante le manovra del hemodialyse artificial. Si le administration de digitalis es urgente, le problema de toxicitate require un semper-vigilante attention.

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THE AIM OF SCIENCE

J. Arthur Thomson

British: professor of natural history, editor and author: 1861-1933

Many of the misunderstandings that have arisen in regard to "science and religion," "science and philosophy," and similar questions are due to a failure to recognize what science aims at—the formulation of things as they are and as they have come to be. The primary aim of science is not to "explain," except in the sense of saying, "this is the outcome of that." It does not inquire into the "why" of things, the purpose or significance of the cosmos.—*The Outline of Science*, Vol. 4, p. 1165. From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

Production of Heart Sounds by the Cardiac Catheter

By FREDERIC L. ELDRIDGE, M.D., AND HERBERT N. HULTGREN, M.D.

Extra heart sounds are frequently produced by the cardiac catheter in the human subject during routine cardiac catheterization. They are associated with a characteristic pressure artefact, which suggests that the sound is produced by back-and-forth movement of the catheter tip across the pulmonic valve. Similar sounds, and also murmurs, can be produced by catheter passage across pulmonary or aortic valves in excised canine hearts. The fact that such artificial sounds can be produced by the intracardiac catheter suggests that some caution must be used in interpreting phonocardiograms obtained during cardiac catheterization.

INCREASED interest in the heart sounds in recent years has led to attempts to obtain better correlation between the sounds and mechanical events within the heart than can be provided by external recording of pulses and sounds. One method is the simultaneous recording of external heart sounds and intracardiac pressures during cardiac catheterization. Recently the recording of intracardiac sounds by means of the intracardiac phonocatheter has been used in an attempt further to refine interpretation.[1, 2] Such methods have proved to be very useful.

For the past year we have been recording simultaneously external heart sounds and intracardiac pressures in a large proportion of routinely catheterized patients. We have observed that heart sounds may be produced by movement of the cardiac catheter within the heart, and that such sounds may lead to errors in interpretation of the phonocardiogram obtained during catheterization. Because of the increasing use of phonocardiography during cardiac catheterization, especially with the intracardiac phonocatheter, we think it of some value to report our findings regarding the incidence, characteristics, and mechanism of production of such catheter-induced heart sounds.

MATERIAL AND METHODS

Of a total number of 132 patients catheterized in this laboratory over a period of a year, 57 will be considered. All these subjects had simultaneous recording of intracardiac pressures and heart sounds during withdrawal of the cardiac catheter from the pulmonary artery to right ventricle and atrium.

Intracardiac pressure pulses were recorded photographically by means of a multichannel mirror oscillograph via the catheter and a Statham strain-gage transducer (P23D). The heart sounds were received by a microphone (Cambridge Instrument Co.) placed on the anterior chest wall in the pulmonic area or along the left sternal border, amplified by means of a low-level amplifier (Tektronics, Inc., Type 122), and recorded by the same oscillographic recorder. With this equipment pressure events on the recording have a delay of no more than 0.01 second in relation to the phonocardiographic events, even with the smallest and largest catheters used.

CLINICAL OBSERVATIONS

The records of 18 of the 57 patients studied were found to show an extra heart sound. In all cases, this was loudest along the left sternal margin at the second or third intercostal spaces. The sound was clearly audible to auscultation over this area.

In 17 of the 18 cases, the extra sound had the following characteristics: 1. It had the same pitch and duration as a second heart sound. 2. It was noted only when the catheter tip appeared to be in the right ventricular outflow tract, or during withdrawal of the catheter from pulmonary artery to right ventricle. In 7 cases, the extra sound was noted only in 1 or 2 heart cycles during the withdrawal, but in the other 10 cases it occurred repeatedly during the period in which the catheter tip seemed to be in the right ventricle. 3. It occurred in early diastole as shown in the example in figure 1. There was no fixed

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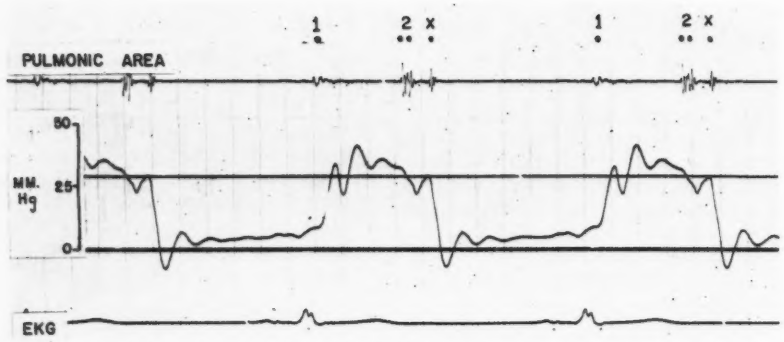

FIG. 1. The extra heart sound (x) in diastole is induced by the cardiac catheter in a human subject. The pressure tracing represents a combination of pulmonary artery pressures (in later systole and in early diastole before the sound) and right ventricular pressures (in diastole following the extra sound and in the first portion of systole). The sharp drop in pressure coincident with the extra sound is due to the sudden pulling back of the catheter tip into the right ventricle.

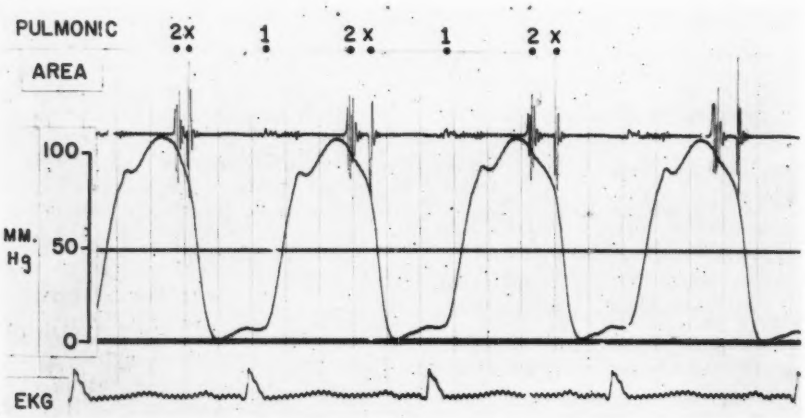

FIG. 2. Extra heart sounds (x) induced by the cardiac catheter, occurring at variable intervals after the second heart sound. Note the variable contour of the "right ventricular" pressure pulse contour, with a sharp drop in pressure occurring at the time of each extra sound.

interval between the second heart sound and the extra sound. From subject to subject and even in the same individual there was often a varying relationship between the second sound and the extra sound (fig. 2). 4. The sound was always associated with a characteristic pressure tracing. This was an artifact in the right ventricular tracing which consisted of prolonged elevation and a sharp drop of pressure in diastole to the diastolic level of the right ventricle (figs. 1 to 4). In every case the extra sound coincided exactly with this pressure drop.

We have interpreted these findings as follows. During end-diastole the catheter tip is in the right ventricular outflow tract, ventricular diastolic pressure being recorded. Systolic contraction of the ventricle pushes the catheter tip through the opened pulmonary valve, so that pressure in the pulmonary artery is recorded. After the second heart sound, in early diastole, the catheter tip remains in the pulmonary artery for a time; but then, as the ventricular cavity enlarges during diastole, it is pulled back through the now closed pulmonary valve into the ventricle, s

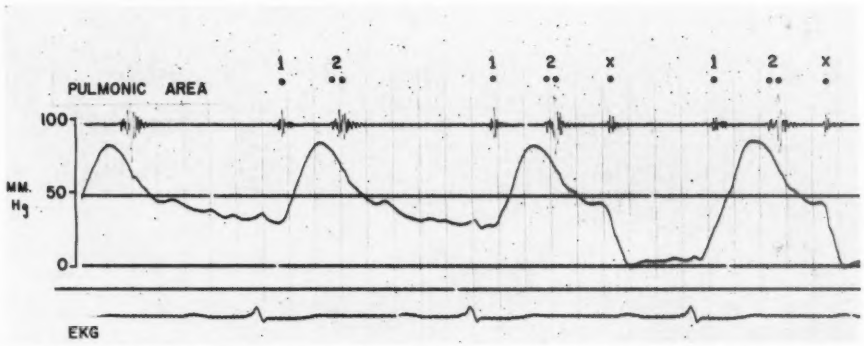

FIG. 3. An extra sound is absent when the catheter tip is fully in the pulmonary artery (first 2 cycles), but it appears when catheter tip passes back and forth between pulmonary artery and right ventricle.

that the recorded pressure drops suddenly. The sound is related to the same events. The presence of the catheter does not prevent a normal second pulmonic heart sound, but withdrawal of the catheter produces an extra valvular sound.

We have on several occasions noted such a back-and-forth movement of the catheter tip across the pulmonary valve during high-speed cineangiocardiographic studies.

Other factors that might have affected the production or incidence of this extra sound were considered. The sound occurred with all sizes (5F to 10F) of cardiac catheters. Age seemed to be no factor, since the range was from 4 to 47 years. The extra sound occurred with a variety of cardiac abnormalities, including 6 with atrial septal defect, 5 with interventricular septal defect, 4 with mitral stenosis, and 2 with primary pulmonary hypertension. There seemed to be no relationship to left-to-right intracardiac shunts, since 6 patients had no shunts, 7 had moderate-to-large shunts, and 4 had balanced left-to-right and right-to-left shunts. The 1 factor that appeared to be of some importance was that of pulmonary hypertension, a pulmonary artery systolic pressure of greater than 40 mm. Hg being present in 12 of the 17 cases, a greater incidence than would be expected from the material usually studied in this laboratory. Nevertheless, the existence of pulmonary hypertension was not essential for the production of the extra sound, 1 subject having a systolic pulmonary pressure of only 26 mm. Hg.

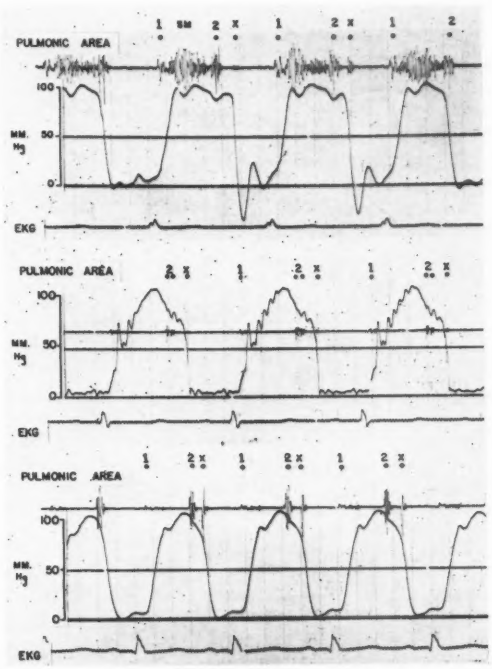

FIG. 4. Sounds and "right ventricular" pressure tracings from 3 human subjects showing appearance of extra heart sound (x) and pressure artifact coincident with sound.

None of the 10 patients with moderate to severe pulmonic stenosis developed this dias-

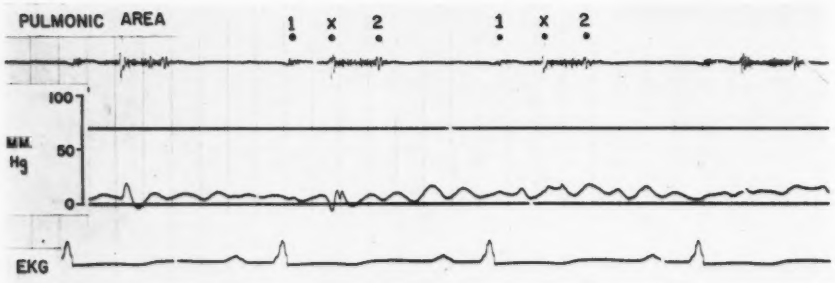

FIG. 5. Sounds and pulmonary artery pressure tracing from a patient with pulmonic stenosis. Note systolic extra heart sound (x), which occurred only when catheter was in pulmonary artery.

tolic sound. It is therefore of interest that the eighteenth patient, who had severe valvular pulmonic stenosis, did show a midsystolic sound (fig. 5). This sound occurred only when the catheter tip was located in the pulmonary artery several centimeters beyond the valve.

In spite of the occasional appearance of a pressure artifact due to the catheter tip's passing from the ventricle to the atrium during systole, no coincident extra sound was noted in any case.

EXPERIMENTAL OBSERVATIONS

In view of the findings in patients, we thought it desirable to attempt the experimental production of heart sounds by means of the cardiac catheter, and to verify the valvular origin of the sound.

1. The intact hearts and great vessels from 2 recently killed normal dogs were used. In each, the pulmonary artery was cannulated and attached by means of plastic tubing to a small reservoir of water. A pressure of approximately 25 to 30 mm. Hg was maintained in the pulmonary artery, which kept the pulmonary valve cusps tightly closed.

Pressures within the right ventricle and pulmonary artery were recorded by means of a cardiac catheter inserted through the right ventricular wall. Sounds were recorded by means of the equipment described above, the microphone being carefully placed over the main pulmonary artery. During the procedure, pressures and sounds were recorded simultaneously while the catheter tip was being moved slowly or rapidly in and out of the pulmonary artery, through the pulmonic valve.

In both hearts the passage of the catheter tip through the pulmonary valve, in either direction, caused loud sounds to occur. An example is shown in figure 6. The high intensity of sound at the pick-up site is demonstrated by comparison with the apex sounds of a normal human adult taken with the same equipment and at the same amplifier setting.

The main factor in the production of the sound seemed to be the setting of the tensed valve cusps into vibration by insertion or withdrawal of the catheter tip. The size of the catheter was unimportant as far as sound production was concerned, as was the position (lateral or central) of the catheter in the valve. The speed of withdrawal was important: when fast, a sharp sound was generated; when slow, no sound was recorded but the presence of the catheter tip in the valve produced pulmonic insufficiency and the associated murmur (fig. 7).

2. A similar experiment was performed with another excised canine heart with use of the aorta valve. Here again, passage of the catheter tip across the valve yielded sharp, loud sounds.

DISCUSSION

It is apparent from these findings that the presence of a catheter in the heart can bring about the production of true valvular heart

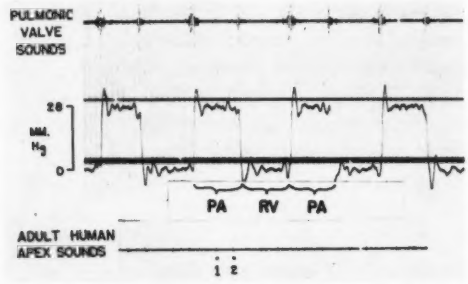

FIG. 6. Sounds generated at the pulmonic valve in an excised dog heart when catheter tip passed rapidly back and forth between right ventricle and pulmonary artery. Pressure tracing shows abrupt fall in pressure as catheter tip passes across closed pulmonic valve. *Lower tracing* of normal adult human apex sounds taken with same equipment and amplification shows the high intensity of the sounds induced in the dog heart.

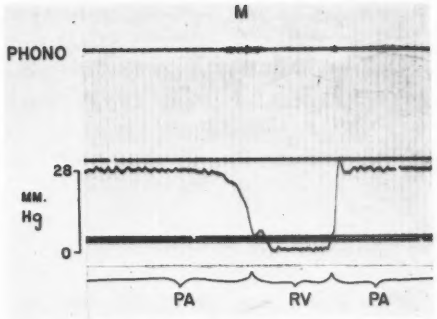

FIG. 7. Tracing showing the murmur of pulmonic insufficiency generated in an excised dog heart by slow withdrawal of the catheter tip from pulmonary artery to right ventricle.

sounds. The coincidence of the pressure artefact and the extra heart sound, and the experimental findings are strong evidence in favor of the postulated mechanism as the cause of the diastolic extra sound found in most of our subjects. Further support comes from the demonstration by high-speed cineangiocardiography of a back-and-forth movement of the catheter tip across the pulmonary valve.

Since sounds were caused in the excised hearts both by insertion and by withdrawal of the catheter across the pulmonary valve, it may be questioned why only withdrawal caused a sound in the human subjects. The explanation undoubtedly lies in the fact that in the excised heart the valve was closed during both insertion and withdrawal, and was therefore capable of producing sound with both, whereas in the beating heart, systolic opening of the valve occurred before ventricular contraction pushed the catheter through, and therefore no sound could be generated.

It is interesting that no diastolic sounds were produced in cases with pulmonic valvular stenosis. We have no definite explanation for this observation, but there are 3 possibilities: 1. The pressure in the pulmonary artery is insufficient to tense the valve cusps enough to produce sound. 2. The rigid valve cusps are not able to vibrate sufficiently to cause audible sound. 3. Because of the narrow valve orifice the catheter tip cannot easily move into and out of the pulmonary artery, and the conditions for the production of the sound are not established. Cineangiocardiographic studies on suitable patients might help to settle this point.

The experimental findings, and the 1 patient with pulmonic stenosis who had a systolic sound, suggest that other sounds and murmurs can be produced by a catheter in the heart. No murmurs attributable to the catheter were recorded externally in any of our human subjects, but it may be that any murmurs produced were of insufficient intensity. The experimental findings demonstrated the striking loudness of the diastolic sound, which was easily recorded in patients.

In view of the increasing use of phonocardiographic technics during cardiac catheterization, one should be aware of the possibility of catheter-induced extra sounds, for under some circumstances the diastolic sound described could be interpreted as a late pulmonic second sound. Although the presence of the pressure artifact, which to our knowledge has not been described before, is helpful in making the proper distinction, many of the phonocatheters in use at the present time do not have a separate lumen for measurement of intracardiac pressures, making this check on the sound events unavailable.

Lewis and co-workers,[2] who have reported on the use of the phonocatheter in man, did not discuss the development of the extra sounds reported here, but did mention that "when the catheter tip was in contact with the inner wall of the heart or valves, loud knocking sounds were obtained."

The fact that such artificial sounds as those described can be produced by the intracardiac catheter suggests that some caution must be used in interpreting the findings of intracardiac phonocardiography in other respects. It is possible, for example, that systolic murmurs recorded in the pulmonary artery could be produced or accentuated by the catheter. In 1 patient, studied in this laboratory, with a stenosis of the right branch of the pulmonary artery, the presence of a catheter in the area of stenosis led to an accentuation of the murmur.

The frequency of extra sounds noted in this study indicates that the back-and-forth movement of the catheter tip across the pulmonary valve is not an unusual occurrence during cardiac catheterization, and, in fact, an additional 5 patients of the 57 studied showed the pressure artifact without recordable sound production. This catheter movement is of some practical importance in routine cardiac catheterization, for what is thought to be a high right ventricular blood sample may in reality be a mixture of ventricular and pulmonary artery bloods. Such a finding in a patient with patent ductus arteriosus might lead one to suspect wrongly a ventricular septal defect or pulmonic insufficiency.

Summary

In 18 of 57 patients who had phonocardiograms recorded during diagnostic cardiac catheterization, an extra heart sound was recorded. In 17 of the 18, the extra sound was in diastole, and could be identified by its timing and its association with a characteristic pressure tracing. Movement of the catheter tip back and forth across the pulmonic valve during the heart cycle is thought to be responsible for production of the sound and the pressure artifact. Experimental studies in excised canine hearts showed that catheter passage across the pulmonary or aortic valves induced similar sounds, and also murmurs.

In an eighteenth patient, one with valvular pulmonic stenosis, catheter movement in the pulmonary artery appeared to be the cause of an extra heart sound in systole. The diastolic sound was heard in none of the 10 patients with pulmonic stenosis.

The fact that such artificial sounds can be produced by the intracardiac catheter suggests that some caution must be used in interpreting phonocardiograms obtained during cardiac catheterization.

The frequency of the back-and-forth movement of the catheter across the pulmonary valve suggests that not uncommonly what is thought to be a high right ventricular blood sample is in reality a mixture of ventricular and pulmonary artery bloods. This would be of some importance in the cardiac catheterization of patients with patent ductus arteriosus.

Summario in Interlingua

In 18 ex 57 patientes, in qui phonocardiogrammas esseva registrate durante diagnostic catheterismo cardiac, un supranumerari sono cardiac esseva registrate. In 17 del 18 casos, ille sono esseva in diastole e poteva esser identificate per le tempore de su occurrentia e per su association con un characteristic curva de tension. Movimentos del puncta del catheter in avante e in retro a transverso le valvula pulmonic durante le cyclo cardiac es considerate como responsabile pro le production del sono e le artefacto de tension. Studios experimental in excidite cordes canin monstrava que le passage de un catheter a transverso le valvula pulmonar o le valvula aortic induceva simile sonos e etiam murmures.

In le dece-octave patiente, qui habeva stenosis del valvula pulmonic, le movimento del catheter in le arteria pulmonar pareva esser le causa de un supernumerari sono cardiac in systole. Le supra-discutite sono diastolic esseva audite in nulle de 10 patientes con stenosis pulmonic.

Le constatation que tal sonos artificial pote sser producite per le catheter intracardiac uggere que certe precautiones debe esser usa- in interpretar phonocardiogrammas obte- ite durante catheterismo cardiac.

Le frequentia del movimento in ante e etro que le catheter executa a transverso le alvula pulmonar suggere que il occurre non nfrequentemente que un specimen de sangu- ne reguardate como de origine dextero-ven- ricular alte es in realitate un mixtura de sanguine ventricular con sanguine de arteria pulmonar. Isto esserea de alicun importantia in le application de catheterismo cardiac al studio patientes con patente ducto arteriose.

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Incidence of the Disease.—As noted long ago by Sir Gilbert Blaine, angina pectoris is a rare affection in hospital practice. Gairdner criticises this statement rather sharply, and yet I think that a majority of hospital physicians would be found to support it. During the ten years in which I lived in Montreal, I did not see a case of the disease either in private practice or at the Montreal General Hospital. At Blockley (Philadelphia Hospital), too, it was an exceedingly rare affection. I do not remember to have had a case under my personal care. There were two cases in my service at the University hospital. During the seven years in which the Johns Hopkins Hospital has been opened, with an unusually large "material" in diseases of the heart and arteries, and with many cases of heart pain of various sorts, there have been only four instances of angina pectoris. You will find the statement in Fagge's Practice (third edition, vol. ii, p. 26) that the "writer has never seen classical angina in hospital practice."

On the other hand, an individual consultant may see within a year more cases than occur in all the hospitals of his town within the same period. In corroboration of this striking contrast between the incidence of angina pectoris in hospital and consulting work I may refer to the statistics of the Edinburgh Royal Infirmary, in which for the two years covered by the Hospital Reports, 1893 and 1894, there were five cases among a total of 8,868 medical cases. Compare with this the personal experience of the distinguished Edinburgh consultant, Dr. Balfour, who, in his recently issued work on the Senile Heart, gives an analysis of ninety-eight cases of angina pectoris seen within ten years. My individual experience embraces a series of sixty cases, forty of which may be regarded as true angina.—William Osler. *Lectures on Angina Pectoris and Allied States,* 1897.

"Peripheral Resistance" in Hypertension Following the Abolition of Local Sympathetic Tone

By Francis S. Caliva, M.D., Jay F. Harris, M.D., and Richard H. Lyons, M.D.

Blood flows of the toe were studied before and after nerve block in normotensive and hypertensive patients, and an estimate of peripheral resistance was made. It was found that in all hypertensive patients there was an increased "peripheral resistance" at rest in the skin of the toe. Following abolition of sympathetic tone, the "resistance" in some individuals fell to a normal level, in others the "resistance" dropped less. The possible significance of these facts is discussed in the light of the etiologic factors responsible for the vasomotor tone.

THE ROLE of the sympathetic nervous system in producing the increased peripheral resistance of hypertension remains unsettled. The problem has been investigated by a number of workers using a variety of technics and approaches, but results have been conflicting.[1-13] Recent work has tended to minimize a neural factor and to ascribe the increased resistance to some type of change in the arterial wall itself.[14, 15]

It occurred to us that the technic of toe plethysmography might lend itself well to the further study of this problem. The tissue studied is mainly of one type, i.e., skin, and the vascular bed is restricted to small vessels. In this way, the varying reactivity of different-sized vessels or vasculature in various tissues is not a complicating factor.

Abolition of sympathetic tone in the toe is easily accomplished by posterior tibial nerve block, a method which leaves little doubt that the vasoconstrictor impulses have been interrupted and interrupted only locally. Also the entire procedure is a simple one and can be done without much discomfort or anxiety on the part of the patient.

Materials and Methods

Blood flows of the toe were measured according to the method of Simeone et al.[16] in 22 normotensive and 43 hypertensive patients. The hypertensive patients had blood pressure readings on the ward regularly at 140/90 or above, and were not receiving antihypertensive medication at the time of study. They ranged in age from 19 to 62, with a mean of 38. The ages of the normal patients were from 18 to 47, with a mean of 32.

In both groups an attempt was made to study patients who clinically exhibited no heart failure or peripheral vascular disease. In a further effort to exclude peripheral vascular disease, no patient whose blood flow following posterior tibial block did not reach a maximum of 6 ml./100 ml. of tissue/min. (minimal normal in our laboratory) was included in either group.

Twenty-five of the patients with elevated blood pressures were diagnosed as "benign essential hypertension." Diagnoses in the others were chronic nephritis in 11 (2 of these with unilateral kidney disease), post-toxemia of pregnancy in 3, malignant hypertension in 2, and pheochromocytoma and thyrotoxicosis, 1 each. The normal persons were, in general, patients without significant disease.

All patients were lightly clad, supine, and lying comfortably on a stretcher in a constant-temperature room (21 C. ± 2 C.). The occlusion cuff was placed at the ankle and no correction was made for this factor in calculating blood flows that were expressed as ml./100 ml. of tissue/min. In each instance the occlusion pressure (usually 40 to 60 mm. Hg) which resulted in the maximum inflow slope was utilized. Brachial artery blood pressures were obtained by auscultation at frequent intervals during the period of observation. The mean blood pressure was calculated as the average of systolic and diastolic readings. The level at which the pressure "stabilized" was used in the calculations for "peripheral resistances."

During the nerve block 4 normotensive patients underwent blood pressure changes that placed their mean pressures at hypertensive levels. However, since these rises were mainly in the systolic pressure, and since the ward determinations had been consistently normal, they were classified as

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TABLE 1.—*Hemodynamic Changes after Nerve Block*

	No.	Before block			After block		
		Mean blood pressure and standard deviation (mm. Hg)	Mean blood flow and standard deviation (ml./100 ml./min.)	Mean "peripheral resistance" and standard deviation	Mean blood pressure and standard deviation (mm. Hg)	Mean blood flow and standard deviation (ml./100 ml./min.)	Mean "peripheral resistance" and standard deviation
Normal	22	98 ± 10.8	.9 ± .64	143 ± 73.2	97 ± 9.9	14.5 ± 5.5	8 ± 3.3
Group 1	30	147 ± 27	.7 ± .15	331 ±274	142 ±24	18.4 ± 6.2	9 ± 3
Group 2	13	176 ± 29.9	.6 ± .26	333 ±128.2	171 ±27.4	8.2 ± 7.8	22 ± 4.9

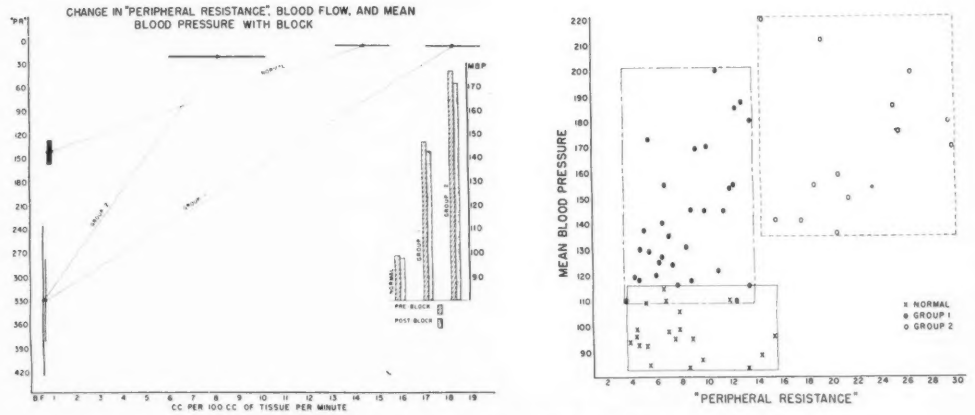

FIG. 1 *Left.* Changes that occurred in the 3 groups of patients before and after posterior tibial nerve block. Center point represents mean values for both "peripheral resistance" and blood flows. Length and thickness of lines extending from the center represent the standard error of the mean of the "peripheral resistance" and blood flows respectively. Mean blood pressures before and after block are plotted separately on right side of graph.

FIG. 2 *Right.* Scattergraph of all "peripheral resistances" after block plotted against mean blood pressure, also after block. Group 1 patients are those with "peripheral resistances" of less than 14.6 and group 2 those with higher values.

the normotensive group. In addition, when 2 known hypertensive subjects were studied, their mean blood pressures were in the normotensive range. Because of their history and previous pressure readings, they were included in the group with high blood pressure.

After fairly constant blood flows had been obtained, a posterior tibial nerve block was performed with 5 ml. of 2 per cent procaine with added hyaluronidase. Completeness of block was tested by loss of sensation over the cutaneous distribution of the nerve. If sensory loss was incomplete, more procaine was injected until the desired result was obtained. An estimation of peripheral resistance was made by dividing the mean blood pressure by the average blood flow before the block and the average of the highest set of readings after the block.[5, 17, 18] No attempt was made to measure venule pressure.

RESULTS

Table 1 and figure 1 summarize the results obtained in these studies.

In the control period, the range of blood flows was not significantly different in either normotensive (.9 ± .64) or hypertensive (.7 ± .15 and .6 ± .26) patients, indicating a difference in peripheral resistance in the 2 types of patients. After nerve block in the normal patients, the flow values increased many times, and the calculated "resistance" fell to low levels (8 ± 3.3).

All the hypertensive patients, however, did not react in the same way to the abolition of local sympathetic tone. While certain of them did demonstrate large increases in flow and

TABLE 2.—*Diagnoses in Groups 1 and 2*

	Group 1	Group 2
Essential hypertension	24	3
Chronic nephritis	2	4
Unilateral renal disease		2
Acute nephritis	1	
Malignant hypertension		2
Post-toxemia	2	1
Thyrotoxicosis	1	
Pheochromocytoma	1*	1†
Total	31	13

*After operation.

†Before operation.

TABLE 3.—*Analysis of Groups 1 and 2*

	Group 1	Group 2
Number of patients	30	13
Sex	14 female 16 male	5 female 8 male
Color	2 Negro 28 white	2 Negro 11 white
Eyegrounds	26 normal or grade I 4 grade III	6 grade I-II 7 grade IV
Renal function	5 abnormalities, 1 test 4 abnormalities, 2 or more tests	2 abnormalities, 1 test 8 abnormalities, 2 or more tests

falls in "peripheral resistance," others exhibited comparatively small increases in flow. In this latter group, the calculated "peripheral resistance" was much higher.

Hypertensive patients were, therefore, subdivided as follows: Group 1, those in whom the "peripheral resistance" following block fell to within 2 standard deviations of the normal subjects, i.e., 14.6, and group 2, the patients whose "resistances" after block were over 14.6.

It can be seen from the table that the control "peripheral resistances" in the hypertensive groups 1 and 2 differed significantly from the normal group ($p<.01$), but not from each other. Following nerve anesthesia, the relatively low mean flows achieved in group 2 were markedly different from those of either group 1 ($p = .01$) or of the individuals with normal pressures ($p = .01$).

Since groups 1 and 2 varied so in their responses, the clinical records of these patients were reviewed and analyzed. These data are summarized in tables 2 and 3.

Group 1 was composed of 16 males and 14 females. Twenty-four were diagnosed as essential hypertension. There were 2 patients with chronic nephritis, 2 with post-toxemia of pregnancy, and 1 each with acute nephritis and thyrotoxicosis. Twenty-six patients in this group had either normal or grade-I eyeground (Keith-Wagener)[19] changes. There were 4 with grade-III changes. Of the renal function tests performed (urinalysis, NPN, PSP, Mosenthal, IVP) only 9 had abnormalities. In 4 of these more than 1 test was abnormal: 3 of these patients had nephritis and the other one had had toxemia of pregnancy.

Group 2 was made up of 13 patients, 5 women and 8 men. Six of the 9 nephritic patients in the series fell into this group as did the 2 individuals with malignant hypertension. The patient with the pheochromocytoma preoperatively had a calculated "peripheral resistance" of 29.5 units and was listed in group 2. About 6 months after surgery, even though he was still hypertensive, his "peripheral resistance" had fallen to 7.6 units and he was now clearly in group 1.

Seven patients in group 2 had eyeground changes classified as grade IV. The other 6 had typical findings of grades I and II. Only 3 patients had no detectable abnormality of renal function.

Both patients with unilateral renal disease were included in group 2. One of these subsequently underwent nephrectomy with no change in blood pressure, but with some fall in "peripheral resistance" (25-15 units). The other patient with unilateral renal disease had been diagnosed ante mortem as malignant hypertension. At autopsy, he was found to have thrombosis of the renal artery with "Goldblatt-type" kidney.

Two nephritic patients in group 2 and in group 1 were markedly anemic. Otherwise

blood viscosity as judged by hematocrits and total protein was within normal limits in all other patients.

It is interesting that all the patients with grade-IV eyeground changes fell into group 2, and there were no patients in this group in whom eyegrounds were normal.

Several of the hypertensive subjects in both groups were studied on more than one occasion in an effort to determine the reproducibility of the method and also to assess more definitely the role of the level of blood pressure in our calculations. Table 4 summarizes these studies and illustrates that, with the exception of the patients who had undergone surgery, the results of repeated testing are quite similar in spite of varying blood pressure levels.

TABLE 4.—*Reproducibility of Method*

Patient	Diagnosis	Date studied	Mean blood pressure (mm. Hg)	"Peripheral resistance"
Z.B.	Unilateral renal disease	8/26/56	186	25
		4/18/57*	178	15
J.B.	Malignant hypertension	3/20/57	175	35
		3/25/57	175	38
T.C.	Essential hypertension	2/14/57	179	37
		2/ 5/57	172	25
		2/ 7/57	180	30
N.R.	Essential hypertension	2/ 2/54	137	12
		5/18/54	162	14
		2/ 4/55	180	12
W.S.	Essential hypertension	7/ 8/53	120	7
		7/15/53	117	6
C.U.	Essential hypertension	11/30/54	168	12
		5/29/56	220	14
A.S.	Post-toxemia	3/21/54	170	30
		7/22/54	145	24
M.M.	Essential hypertension	4/ 7/57	155	7
		4/15/57	123	5
H.G.	Essential hypertension	4/18/52	127	10
		4/11/53	119	11
R.C.	Pheochromocytoma	5/16/56	185	30
		7/17/56†	140	21
		9/16/56*	125	8
R.M.	Essential hypertension	2/19/54	136	7
		5/21/54	170	5
N.V.	Acute nephritis	7/20/53	145	10
		8/19/53	154	10
		6/17/54‡	127	6
		6/11/54‡	119	4

*After surgery.
†Dibenzyline therapy.
‡Recovered.

DISCUSSION

It is fully recognized that the term "peripheral resistance," as we have used it, can refer to only a very crude estimate of the actual physiologic resistance. To obtain a more precise figure would have required measurements of both toe artery and vein pressures.

Further accuracy could have been obtained in control blood flows if the occluding cuff had been placed closer to the toe cup than the ankle. However, the large flows after block might not have been correctly measured by this method.[20] Since we were primarily interested in blood flows after block and only incidentally in the controls, we chose to keep the cuff at the ankle.

Each of the aforementioned, though recognized, are constant errors which do not interfere with a comparison between the various groups. One possible exception is the measurement of small vein pressures. There is some evidence, accumulated in our laboratory, that the small-vein pressure in the toe rises following posterior tibial nerve block.[21] Since this is presumably due to the opening of arteriovenous shunts and a direct passage of high pressure arterial blood into the veins, the vein pressure might rise in proportion to the level of the existing arterial pressure. This, then, would not be a constant, but would vary from patient to patient according to the systemic blood pressure. On the other hand, even were this true, the new figures certainly would not be great enough to effect the large and definite differences that have been demonstrated between the groups.

Since there was considerable variation in mean blood pressure among the patients, a scattergraph was made of all resistances after block plotted against mean blood pressure (fig. 2). It is obvious from this graph that the group variation in "resistance" is not merely a reflection of differences in blood pressure.

Our figures are in agreement with those of many other workers with respect to resting blood flows.[1, 12, 22] There can be little question that in hypertension, blood flow of the skin is within normal limits. The skin, and the toe in particular, therefore, participate in the increased vascular resistance in the patients with elevated blood pressure.

On the other hand, our data do differ from work showing that peripheral resistance in hypertensive patients cannot be reduced to normal levels.[4, 5, 9] The patients included in group 1, after abolition of local sympathetic tone, all had calculated "resistances" that fell within the same range as that of the normotensive subjects. These were individuals who, in general, had fewer evidences of involvement elsewhere, viz., eyeground and kidney. Two patients in this group have died in a 3-year period.

This group stands in contrast to group 2 with "high resistances." Structural vessel changes as suggested by Conway,[15] Mendlowitz,[14] and others[23] may well have been present in these patients. Their blood flows were low, their eyeground changes were advanced, and a large proportion showed definite impairment of renal function. Half of these patients have died in 3 years.

We think, then, that our data suggest a basic difference between various types and stages of hypertension. At least patients would seem to vary with respect to arterial circulation to the toe following abolition of sympathetic tone. There are some hypertensive patients with little or no renal or eyeground changes in whom the increased peripheral resistance in the toe is primarily on a neurogenic basis. This confirms some of the earlier work of Mendlowitz[12] done on fingers and employing another technic to abolish sympathetic tone.

The high "resistances" in group 2 may have been due to either of the following possibilities: (1) structural vascular changes which may or may not be reversible, and (2) pressor activity other than neurogenic. We are unable to say which of these possibilities is the more likely.

Summary

The vessels of the toe participate in the increased peripheral resistance found in hypertension.

Following sympathetic block, hypertensive subjects can be divided into 2 groups: (1) those in whom resistance falls into normal levels and (2) those in whom it does not.

Patients in group 2 in this series were those in whom the hypertensive process was obviously more severe as evidenced by eyeground and renal changes and prognosis for life.

It is suggested that changes in the wall of the blood vessel may well have been present in group 2, but were probably absent in group 1, where neurogenic vasospasm seemed to play a dominant role.

Acknowledgment

The authors wish to acknowledge the technical assistance of Miss Madeline Tuori, R.N. and Mr. Paul Gabel, B.S.

Summario in Interlingua

Le vasos del digitos del pede participa in le augmentate resistentia peripheric que es trovate in hypertension.

Post bloco sympathic, hypertensivos forma 2 gruppos: (1) Subjectos in qui le resistentia descende a nivellos normal e (2) subjectos in qui iste evento non occurre.

In le serie de patientes del presente reporto, gruppo 2 consisteva del subjectos in qui le processo hypertensive esseva obviemente plus sever, a judicar per alterationes del fundo ocular e del renes e per le prognose del curso futur.

Es suggerite que alterationes in le pariete vascular esseva probabilemente presente in gruppo 2 sed absente in gruppo 1, ubi vaso spasmo neurogene pareva haber un rolo dominante.

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Capacity of Human Coronary Arteries

A Postmortem Study

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With the technical assistance of Olga F. Connolly

A postmortem study of the capacity of the coronary arteries of 100 human hearts is presented. The volume of Schlesinger's barium sulfate-gelatin injection mass entering the coronary arterial tree under standard conditions was taken as a measure of its capacity. The factors analyzed include the weight of the heart in the normal and diseased state, the cross-sectional dimensions of the main coronary arteries near their origins, and the sex, age, and nutrition of the subjects.

THE INFORMATION available concerning the capacity of the coronary arterial tree is derived from such collateral data as the perfusibility of its bed[1] and the dimensions of its main components.[2, 3]

Direct observations on the total capacity of the human coronary arteries are reported here. The relationship to the weight of the normal and the diseased heart, and possible variations attributable to sex, age, and nutrition are the aspects dealt with in the analyses. The volume capacity of the coronary arterial tree is also correlated with the cross-sectional dimensions of its main components near their origins.

Method and Materials

An elaboration of a method devised by Schlesinger[4] was used in this investigation. The coronary arteries of hearts obtained at autopsy were injected with a radiopaque mass, laid out in 1 plane, visualized roentgenographically, and dissected. The radiopaque mass consists of barium sulfate in a menstruum of gelatin; it remains confined to the arterial side of the circulation and penetrates regularly to arterioles 40 to 50 μ in diameter. According to Schlesinger and from our own observations it advances only inconstantly into vessels of smaller size.[5] By leaving the capillaries and veins uninjected the primary distribution and ultimate terminations of the coronary arterial tree were delimited. A pneumatic apparatus in which the pressure may be accurately controlled was employed for injection. The injection pressure was gradually raised to 200 mm. Hg, was maintained at that level for 5 minutes, and then the injection was terminated. Clamps placed about the cut ends of the great vessels prevented leaks.

The capacity of the coronary arteries was determined by the amount of injection mass taken up under the standard conditions outlined above. Burets were used as reservoirs. In preliminary experiments it was found that the barium sulfate-gelatin mixture tended to adhere to the sides of the buret rendering volumetric readings difficult to take. To obviate this difficulty, a long column of silicone of low viscosity (Dow Corning, 5 c.s.) was superimposed on the injection mass in the burets, and its fall was taken as a measure of the amount of injection mass entering the coronary arteries. Roentgenograms of the ventricles sliced in coronal fashion established the completeness of injection of the fine arterial branches.

The mean internal diameters of the left descending, left circumflex, and right coronary arteries were determined from the angiogram of the "unrolled" heart. For this purpose, a measuring magnifier calibrated at 0.01-cm. intervals was used. The "unrolling" of the heart was accomplished by a series of incisions which leaves the interventricular septum intact.[6] The x-ray values employed for all hearts were 100 ma., 4[illegible] kv., 0.75 second, and 40 inches (tube to film). Measurements were confined to the first centimeter of each artery. The sum of the cross-sectional areas of all 3 vessels was then derived from the diameters obtained.

The analysis of the capacity of the coronary arteries was limited to 100 out of a total of over 200 hearts processed. Absence of leaks during injection and complete filling of the coronary arteries constituted the 2 criteria for selection.

The cross-sectional areas of the 3 coronary arteries were obtained in 50 of these 100 hearts

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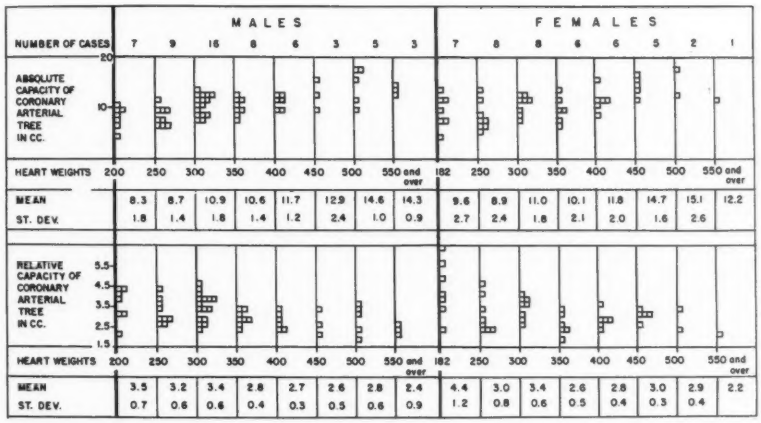


FIG. 1. The capacity of the coronary arterial tree of 100 human hearts grouped according to heart weight and sex.

Distortion of the lumen or mural calcification in the arterial segments studied precluded reliable measurements in the others.

OBSERVATIONS

The capacity of the coronary arteries in cubic centimeters is expressed both as actual values (absolute capacity), and in terms relative to 100 Gm. of heart weight (relative capacity). The latter was obtained by dividing the capacity of the coronary arteries by the weight of the heart and multiplying the ratio so derived by 100. The recorded weight of the heart excludes the injection mass within the coronary arteries and includes usually less than 1.5 cm. of the aorta and pulmonary artery.

The results of the analyses are presented in the form of comparisons of group means, variability, and frequency distributions. The level of significance adopted was a probability of 0.05.

Heart Weight and Sex

Figure 1 presents the distribution of the absolute and relative capacities of the coronary arteries of 100 human hearts grouped according to weight and sex.

There were 57 male hearts weighing from 208 to 620 Gm. and 43 female hearts weighing between 182 and 552 Gm. Thirty-seven hearts (17 males, 20 females) exceeded the upper limits of normal size arbitrarily set at 399 Gm. for male, and 349 Gm. for female hearts.

The capacity of the coronary arteries varied greatly from heart to heart. The absolute capacities ranged from 5.3 to 17.7 ml. among males, and from 4.7 to 17.7 ml. among females. The corresponding values for the relative capacities were from 1.88 to 4.50 ml./100 Gm. for males and from 1.95 to 6.42 ml./100 Gm. for females, respectively.

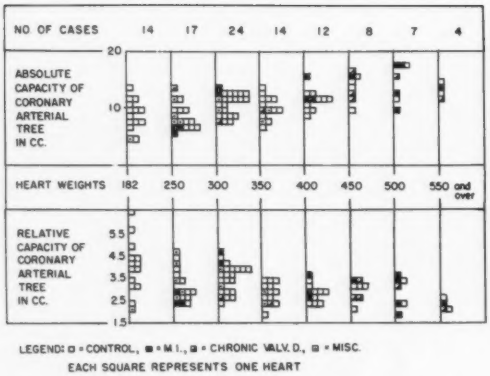
In both males and females, a rise in the weight of the heart was associated with an increase in the capacity of the coronary arteries. However, the enlargement of the coronary arteries appeared not to keep pace with that of the cardiac mass. Although heavy hearts gave larger absolute capacities than small hearts (fig. 1*A*), the capacity of the coronary arteries per 100 Gm. of heart weight was actually less in the heavy hearts than in the small ones (fig. 1*B*).

Within each weight class, differences in the absolute and relative capacities of the coronary arteries between males and females were negligible.

Cardiac Pathology

All hearts in the series were grouped into 4 pathologic categories:

A. Myocardial Infarcts: Fourteen Hearts (8 Males, 6 Females). This group contained



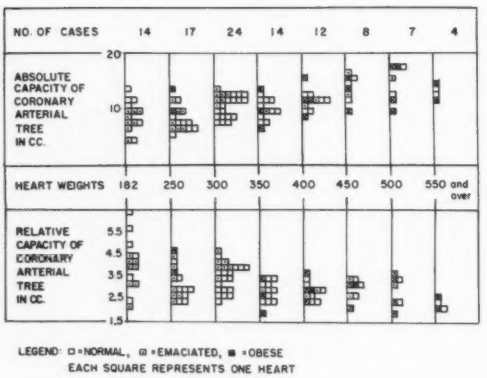


FIG. 2 *Left.* The capacity of the coronary arterial tree of 100 human hearts grouped according to heart weight and pathologic category.

FIG. 3 *Right.* The capacity of the coronary arterial tree of 100 human hearts grouped according to heart weight and nutritional category.

13 healed and 5 recent infarcts. Twenty-five separate occlusions were demonstrated in the coronary arteries of 12 hearts. In 2, infarction was associated with stenosing coronary atherosclerosis without occlusion.

B. Chronic Valvular Disease: Seven Hearts. Conspicuous deforming lesions of the valves were present in 3 hearts with aortic stenosis (1 male, 2 females) and 4 with mitral stenosis (1 male, 3 females).

C. Miscellaneous Forms of Cardiac Pathology: Ten Hearts. Comprising this group are 4 hearts with acute bacterial endocarditis (1 male, 3 females), 2 with nonbacterial endocarditis (2 females), and 4 with cardiac mural thrombosis not associated with valvular disease or myocardial infarction (2 males, 2 females).

D. Hearts Not Belonging to Any of the Above Categories: Sixty-Nine Hearts. (44 Males, 25 Females). This control group comprised normal hearts as well as hearts with such abnormalities as cardiac hypertrophy; coronary atherosclerosis not associated with severe stenosis or occlusion of the coronary arteries; focal fibrosis near the annulus fibrosus, in the tips of papillary muscles, or the vicinity of blood vessels; nondeforming atherosclerosis of the valves or valve rings; and patches of epicardial thickening.

The distribution of the absolute and relative capacities of the coronary arteries of all hearts, rearranged according to weight and pathologic category, is shown in figure 2.

The presence of cardiac pathology other than hypertrophy appeared not to alter appreciably the capacity of the coronary arteries. Within each weight class no significant difference in the mean absolute or relative capacity of the coronary arteries was established between hearts with and those without pathology, or between hearts with and those without myocardial infarction (table 1).

Age

The mean ages for males and females in the series were 80.9 years and 68.4 years, respectively. Eighty-nine subjects (48 males, 41 females) fell between the sixth and ninth decades. Thirty-eight (20 males, 18 females) were in the eighth decade. The youngest heart was from a boy of 13 years; the oldest, from a man of 95 years.

The age distribution of all subjects grouped according to heart weight is listed in table 2. The differences in mean age of subjects distributed among the various (heart) weight classes were statistically negligible.

In order to evaluate further whether or not age has any influence on the capacity of the

TABLE 1.—*The Capacity of the Coronary Arterial Tree in 100 Human Hearts Grouped According to Heart Weight and Pathologic Category*

Pathologic category		Heart weight (Gm.) 182 to 249	250 to 299	300 to 349	350 to 399	400 to 449	450 to 499	500 to 549	550 and over
Absolute capacity of the coronary arterial tree (ml.)									
	No. of cases	13	9	19	11	9	4	2	2
Control	Mean	9.3	8.8	10.9	10.7	11.3	13.8	14.6	14.3
	St. Dev.	2.2	1.4	1.5	1.8	1.4	2.3	3.1	1.0
	No. of cases	1	8	5	3	3	4	5	2
All abnormals	Mean	5.3	8.9	11.2	9.3	13.0	14.3	14.8	13.2
	St. Dev.	—	2.4	2.6	0.7	2.4	1.8	3.1	1.4
	No. of cases	0	3	2	0	3	1	4	1
Myocardial infaret	Mean	—	6.9	13.0	—	13.0	15.6	14.4	14.3
	St. Dev.	—	0.5	0.5	—	2.4	—	3.4	—
	No. of cases	0	0	1	1	0	3	1	1
Chronic valvular disease	Mean	—	—	7.9	9.8	—	13.9	16.4	12.2
	St. Dev.	—	—	—	—	—	2.0	—	—
	No. of cases	1	5	2	2	0	0	0	0
Misc.	Mean	5.3	10.1	11.1	9.1	—	—	—	—
	St. Dev.	—	2.3	1.3	0.8	—	—	—	—

Pathologic category		Heart weight (Gm.) 182 to 249	250 to 299	300 to 349	350 to 399	400 to 449	450 to 499	500 to 549	550 and over
Relative capacity of the coronary arterial tree (ml.)									
	No. of Cases	13	9	19	11	9	4	2	2
Control	Mean	4.1	3.1	3.4	2.8	2.7	2.8	2.8	2.4
	St. Dev.	1.0	0.7	0.5	0.5	0.3	0.4	0.5	0.2
	No. of cases	1	8	5	3	3	4	5	2
All abnormals	Mean	2.1	3.1	3.6	2.5	3.0	2.9	2.8	2.2
	St. Dev.	—	0.8	0.7	0.2	0.4	0.3	0.6	0.6
	No. of cases	0	3	2	0	3	1	4	1
Myocardial infaret	Mean	—	2.5	4.3	—	3.0	—	2.8	2.4
	St. Dev.	—	0.2	0.2	—	0.4	—	0.6	—
	No. of cases	0	0	1	1	0	3	1	1
Chronic valvular disease	Mean	—	—	2.5	2.4	—	2.8	3.1	2.2
	St. Dev.	—	—	—	—	—	0.4	—	—
	No. of cases	1	5	2	2	0	0	0	0
Misc.	Mean	2.1	3.5	3.4	2.5	—	—	—	—
	St. Dev.	—	0.7	0.4	0.2	—	—	—	—

oronary arteries, a group of 5 normal hearts epresenting one extreme of age in our series as contrasted with a similar group of comarable weight representing the other exeme (table 3). No significant difference in ean absolute and relative capacities of the oronary arteries was observed between the groups.

utrition

Figure 3 presents the distribution of the solute and relative capacities of the coronary arteries of all hearts, regrouped according to heart weight and nutritional status of the subjects.

Twenty-eight subjects were emaciated, 18 were obese, and 54 were nutritionally normal at the time of death.

Among hearts weighing from 300 to 349 Gm., the coronary arteries of those from emaciated subjects had significantly larger absolute and relative capacities than the coronary arteries of those from the nonemaciated. Within each of all other weight classes, the

TABLE 2.—*Age Distribution of 100 Subjects Grouped According to Heart Weight*

Age by decades	Heart weight (Gm.) 182 to 249	250 to 299	300 to 349	350 to 399	400 to 449	450 to 499	500 to 549	500 and over	Total
Tenth	—	—	2	—	—	—	—	—	2
Ninth	1	3	5	1	4	3	2	—	19
Eighth	4	7	6	7	6	3	3	2	38
Seventh	4	2	5	3	—	1	1	—	16
Sixth	4	1	2	3	2	1	—	2	15
Fifth	—	1	2	—	—	—	—	—	3
Fourth	—	2	1	—	—	—	—	—	3
Third	—	—	—	—	—	—	1	—	1
Second	1	1	1	—	—	—	—	—	3
First	—	—	—	—	—	—	—	—	—
No. of cases	14	17	24	14	12	8	7	4	100

TABLE 3.—*Data for the Comparative Study of the Coronary Arterial Capacities of Normal Hearts from Young and Old Subjects*

Young					Old				
Age (yr.)	Sex	Heart Wt. (Gm.)	Capacity (ml.) Absolute	Relative	Age (yr.)	Sex	Heart Wt. (Gm.)	Capacity (ml.) Absolute	Relative
13	M	256	9.5	3.73	82	M	305	9.9	3.25
16	F	182	11.7	6.42	83	M	250	9.9	3.96
18	M	307	10.9	3.55	83	F	289	7.0	2.43
30	F	288	8.2	2.85	88	F	238	8.0	3.36
34	M	318	9.4	2.95	90	M	308	7.8	2.53
Mean ± S.D.									
22±8		270±29	9.9±1.1	3.9±1.3	85±3		278±49	8.5±1.4	3.1±1.8

mean absolute and relative capacities of the coronary arteries of hearts belonging to the 3 nutritional categories were of the same order of magnitude (table 4).

Cross-sectional Areas of the Coronary Arterial Lumens

The 50 hearts on which measurements of the coronary arterial lumens were made were from 33 males, age 13 to 95 years, and 17 females, age 16 to 88 years. The average age for males was 63.2 ± 20 years (standard deviation) and for females, 62.4 ± 13 years.

Coronary atherosclerosis was slight or absent in all cases. There were no hearts with myocardial infarction.

The heart weights ranged from 182 to 550 Gm. There were 37 normal-sized hearts among which were 2 with acute bacterial endocarditis, 2 with nonbacterial endocarditis, 1 with cardiac mural thrombosis, and 1 with mitral stenosis. Hypertrophy was present in 13 hearts, attributed to aortic stenosis in 2, to mitral valvular disease in 1, and to hypertension in 10.

The sums of the cross-sectional areas of the coronary arterial lumens ranged from 18.05 to 45.89 mm.^{2} The corresponding values for the capacity of the coronary arteries were 7.5 to 17.7 ml.

The sums of the cross-sectional areas of the major coronary arteries of hypertrophic hearts were significantly larger (mean ± st. dev. : 36.76 ± 8.8 mm.^{2}) than those of normal-sized hearts (mean ± st. dev. : 29.54 ± 7.0 mm.^{2}) (fig. 4).

TABLE 4.—*The Capacity of the Coronary Arterial Tree in 100 Human Hearts Grouped According to Heart Weight and Nutritional Category*

Absolute capacity of the coronary arterial tree (ml.)

Nutritional category		Heart weight (Gm.) 182 to 249	250 to 299	300 to 349	350 to 399	400 to 449	450 to 499	500 to 549	550 and over
	No. of cases	6	8	17	10	6	3	2	2
Normal	Mean	10.1	8.2	10.4	10.4	11.7	14.2	15.1	13.8
	St. Dev.	2.9	1.6	1.8	1.5	1.6	1.7	2.6	0.5
	No. of cases	8	7	7	1	2	2	1	0
Emaciated	Mean	8.2	8.7	12.2	10.4	11.3	15.0	16.6	—
	St. Dev.	1.5	1.5	0.8	—	0.7	1.6	—	—
	No. of cases	0	2	0	3	4	3	4	2
Obese	Mean	—	11.6	—	10.4	12.1	13.3	14.2	13.8
	St. Dev.	—	2.1	—	2.7	2.4	2.5	3.5	1.6
	No. of cases	14	17	24	14	12	8	7	4
All cases	Mean	9.0	8.8	10.9	10.4	11.7	14.0	14.7	13.8
	St. Dev.	2.4	2.2	1.8	1.7	1.7	2.2	3.1	1.1

Relative capacity of the coronary arterial tree in (ml.)

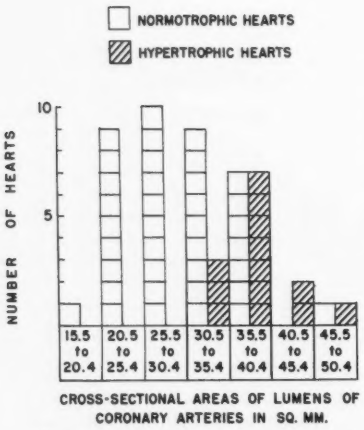
Nutritional category		Heart weight (Gm.) 182 to 249	250 to 299	300 to 349	350 to 399	400 to 449	450 to 499	500 to 549	550 and over
	No. of cases	6	8	17	10	6	3	2	2
Normal	Mean	4.5	2.8	3.2	2.8	2.7	2.9	2.9	2.3
	St. Dev.	1.3	0.6	0.6	0.4	0.3	0.3	0.4	0.1
	No. of cases	8	7	7	1	2	2	1	0
Emaciated	Mean	3.6	3.2	3.9	2.8	2.7	3.0	3.1	—
	St. Dev.	0.7	0.7	0.3	—	0.2	0.3	—	—
	No. of cases	0	2	0	3	4	3	4	2
Obese	Mean	—	4.1	—	2.6	2.9	2.7	2.7	2.4
	St. Dev.	—	0.4	—	0.8	0.5	0.5	0.7	0.3
	No. of cases	14	17	24	14	12	8	7	4
All cases	Mean	4.0	3.1	3.4	2.7	2.8	2.9	2.8	2.3
	St. Dev.	1.1	0.3	0.2	0.4	0.4	0.4	0.6	1.4

A significant positive rectilinear correlation was established between the sums of the cross-sectional areas of the major coronary arteries and the capacities of the coronary arterial tree (coefficient of correlation: 0.64) (fig. 5).

DISCUSSION

Data provided by this investigation seem to establish the fact that the capacity of the human coronary arteries increases with the weight of the heart regardless of cause of hypertrophy, associated cardiac abnormality, or sex, age, and nutritional state of the subject. The exact mechanism by which enlargement of the coronary arteries is brought about remains to be investigated. At least in effect the phenomenon appears to be adaptive, the capacious coronary arterial tree satisfying, to some extent, the demands of the hypertrophied heart for an augmented blood supply.

The evidence seems to indicate that the requirements of the hypertrophic heart may not be fully met in every instance. The ability of the coronary arterial tree to enlarge appeared to vary from heart to heart, and on the average, such enlargement did not keep



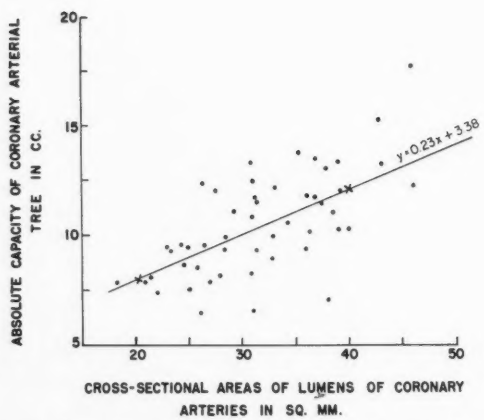


FIG. 4 *Left.* The distribution of the sums of the cross-sectional areas of the lumens of the main coronary arteries in 37 normal-sized and 13 hypertrophic human hearts.

FIG. 5 *Right.* Regression of the capacity of the coronary arterial tree on the sum of the cross-sectional areas of the lumens of the main coronary arteries for 50 human hearts.

pace with the increase in cardiac mass. It has been contended that the potentialities of the heart both for work and for growth vary directly with the available blood supply.[7] If this be granted, then the suggestions may be made: (a) that the disproportion between the capacity of the coronary arteries and the size of the heart may constitute part of the anatomic substrate of the reduced functional reserve in cardiac hypertrophy; and (b) that the degree of enlargement which the coronary arterial tree is capable of attaining may help predetermine the maximum limits of hypertrophy allowed a given heart. It should be pointed out, however, that others have denied the fundamental importance of vascular insufficiency as a factor in the production of myocardial failure in hypertrophic hearts without coronary atherosclerosis.[1, 2]

Our findings relating to hearts with normal vessels confirm the observation that the main coronary arteries enlarge with the heart,[2] and also justify the assumption that the dimensions of the coronary arteries near their origins constitute a fair index of the capacity of the coronary arterial tree as a whole.[3]

An altogether different situation seems to prevail among hearts with severe coronary atherosclerosis. Although there can be little doubt that the lumens of the main coronary arteries were reduced in hearts of our series with coronary narrowings and occlusions, nevertheless, the capacity of the entire coronary arterial tree in these hearts was of the same magnitude as that of hearts in the same weight class with normal vessels. Thus, it would seem that some sort of balance may be struck between the diminution in size of the large coronary arteries and an increase in capacity of other components of the coronary arterial tree. Enlargement of preexisting arterial anastomoses and the development of new ones are known to follow nonfatal restrictions imposed on the coronary arteries.[4] It is not clear from our study whether the presence of such anastomoses accounts in full or only in part for the maintenance of the status quo with respect to coronary arterial volumes in hearts that develop coronary atherosclerosis.

Our findings relating to a decrease in the relative capacity of the coronary arteries in cardiac hypertrophy appear to have been anticipated by the kerosene perfusion experiments on dead hearts performed by Doc[illegible].[1] His conclusions and ours are at variance, however, with respect to the influence of age.

On the basis of a diminished perfusibility of small old hearts he concluded that the coronary bed is reduced in these hearts. In our study the capacity of the coronary arteries in the senile was no smaller than that in the young.

To our view, the above discrepancy in our respective results may be more apparent than real. There seem to be some grounds for the suspicion that the diminished perfusibility of old hearts may not be due to a reduction in the capacity of the coronary bed. It is well known that with age, the coronary arteries became increasingly tortuous.[8] In moving liquids, deviations from a straight-line motion occasion some loss in energy and pressure. The loss is greater in vessels with sharp bends than in vessels of the same caliber with easy ones. It is more in a series of reflex bends than in one in which the curvature is continuous.[9] It would appear that a heightened resistance to flow attributable solely to the exaggerated tortuosity of the coronary arteries in the aged heart can, to a large extent, account for the diminished perfusibility of these hearts despite the fact that the volume capacity of the coronary arteries may not be reduced.

Indeed, since senescence generally involves arterial dilatation, elongation, and increased tortuosity (senile vascular ectasia), we are constrained to account for the fact that the coronary arterial capacities in the aged heart appeared to be no larger than in the young. Two possible reasons may be cited. First, the capacity of the coronary arteries as determined in this study represents in part the ratio between the resisting powers of the coronary arterial walls and the pressure to which they were subjected from within. Inasmuch as identical injection pressures were used for all hearts, the thinner-walled and more distensible coronary arteries of young hearts may have expanded more than those of the old, thus minimizing whatever differences in capacity might be due to age. A second and perhaps more important reason applies also to the influence of nutrition and is discussed below.

Atrophy of the blood vessels may occur in connection with atrophy of a particular organ or as part of the generalized atrophy of malnutrition or senescence.[10] The contention has been made that the coronary arteries do not atrophy with the heart[11] and are therefore exceptions to the rule. Our findings seem to indicate otherwise. Evidence has been presented that in cachexia the heart mass is reduced to a greater degree than the body mass[12] and that in atrophy the heart is reduced in size frequently to two thirds or one half the normal.[11] It is probably safe to assume therefore that in our series the hearts of emaciated subjects were included in (heart) weight classes smaller than that they were in prior to emaciation. If the capacity of the coronary arteries remains unaffected by the nutritional state of the subject, the values for the coronary arterial capacities of emaciated hearts should be larger than those of the nonemaciated in the same (heart) weight class. This in general we found not to be true. Thus it would seem that despite the presence of senile vascular ectasia in some hearts from old cachectic subjects, in most instances the loss in cardiac mass was accompanied by a proportionate reduction in the capacity of the coronary arterial tree.

Summary and Conclusions

A postmortem study of the volume capacity of the coronary arteries in 57 men and 43 women is presented.

The amount of Schlesinger's barium sulfate-gelatin injection mass entering the coronary arterial tree under standard conditions was taken as a measure of its capacity.

1. The capacity of the coronary arteries increases with the weight of the heart.

2. The relationship between the capacity of the coronary arteries and the cardiac weight is not directly influenced by (a) the presence or absence of cardiac abnormalities other than hypertrophy, or (b) the sex, (c) age, and (d) nutritional status of the subject.

3. In cardiac hypertrophy the increase in the coronary arterial capacity does not keep pace with the cardiac mass.

4. In hearts with normal coronary arteries the capacity of the coronary arterial tree varies in direct proportion to the dimensions of the main coronary arteries near their origins.

5. In hearts with severe coronary atherosclerosis the over-all capacity of the coronary arterial tree may be maintained despite the diminution in size of its larger components.

6. In hearts from emaciated subjects the capacity of the coronary arteries is generally reduced in proportion to the loss in cardiac mass.

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Summario in Interlingua

Es presentate un studio post morte del capacitate volumetric del arterias coronari de 57 homines e 43 feminas.

Le proportion del massa injicite de sulfato de barium a gelatina de Schlesinger que penetra le vasculatura coronari sub conditiones standard esseva acceptate como mesura de su capacitate.

1. Le capacitate del arterias coronari cresce con le peso del corde.

2. Le relation inter le capacitate del arterias coronari e le peso del corde non es influentiate directemente per (a) le presentia o absentia de anormalitates cardiac altere que hypertrophia, (b) le sexo del subjecto, (c) su etate, e (d) su stato nutritional.

3. In hypertrophia cardiac, le augmento del capacitate del arterias coronari non es proportional al augmento del massa cardiac.

4. In cordes con normal arterias coronari, le capacitate del vasculatura coronari varia directemente in proportion con le dimensiones del major arterias coronari presso al sito de lor origine.

5. In cordes con sever atherosclerosis coronari, le capacitate total del vasculatura coronari pote esser mantenite in despecto de diminutiones in su componentes major.

6. In subjectos emaciate, le capacitate del arterias coronari es generalmente reducite in proportion al perdita de massa cardiac.

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Vasomotor Responses to Exercise in the Extremities of Subjects with Vascular Disease

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With the technical assistance of Gordon Gilbert, B.S., and Raleigh Wheeler, B.S.

Response of peripheral blood flow was studied in subjects of various age groups with and without vascular disease. Under constant environmental conditions, the skin-muscle distribution of total flow to the lower extremity showed the following trend. In young healthy adults the muscles get a somewhat higher share; in elderly persons without vascular disease the distribution is about equal; in patients with nongangrenous obliterative arteriosclerosis the skin is favored over the muscle. Exercise increases total flow in all groups, but does not alter the distribution. Sympathectomy does not seem to influence response to exercise.

EVIDENCE is lacking that neurogenic vasomotor impulses cause the dilatation of small muscle vessels during exercise, while evidence exists for metabolic or humoral vasodilator mechanisms.[1-5] It has been shown in animals that splanchnic constriction may precede the commencement of muscular effort but does not contribute to a shift of blood flow from the splanchnic to the muscular vascular bed, since no subsequent change in the degree of constriction occurs.[6, 7]

Spalteholz[8] explained an increase in blood flow following the contraction of skeletal muscle by anatomic distribution: The small blood vessels and capillaries in the muscle run parallel to the cylindrical muscle fibers; when the muscle fiber contracts, more space is given to the vessels, and thus resistance to blood flow is decreased. Rein and co-workers[3] explained the increase in blood flow following a muscular contraction by the liberation of a chemical vasodilator substance, and assumed that during contraction the resistance to blood flow in the skeletal muscle diminished.

Anrep[1] proved experimentally that during the muscular contraction the arterial in-flow to the muscle is actually stopped, and interpreted this phenomenon as vasocompression produced by the contracting muscle fiber. Each contraction is, however, followed by vasodilatation, and the blood flow rapidly increases well above resting values.[1] Barcroft and his co-workers[9-11] showed that basal blood flow to the muscles is regulated by the vasomotor centers, but that this central regulation is not responsible for the circulatory changes occurring during activity. Barcroft therefore considered it likely that there may be 2 separate circulations in the skeletal muscle, one controlled by the vasomotor centers and the other by a metabolic mechanism. Saunders and his co-workers[12] have supplied a rather impressive anatomic basis for this assumption in microscopic x-ray evidence for the existence of 2 separate sets of vasculature in the muscle, which makes Barcroft's theory very probable.

A study of vascular responses to exercise in the lower extremity of man is reported here. Efforts to establish a suitable way of exercising the calf muscles of a leg and to measure plethysmographically the changes occurring in blood flow thereafter met with considerable difficulties. Finally, a method of fairly well controlled exercise within the casement of the large limb—plethysmograph[13] was devised, which is described under "methods." A number of experiments on patients with obliterative arteriosclerosis could not be completed because the onset of pain precluded the conclusion of exercise.

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TABLE 1.—*Total Blood Flow of Foot and Leg in Response to Exercise (ml./100 ml. tissue/min.)*

	Young adults	Elderly adults	Elderly adults with obliterative arteriosclerosis	Arteriosclerosis after sympathectomy
Total number of cases	11	13	7	5
Average basal blood flow	14.1	10.4	6.6	10.3
Range of basal flow	4.5-24.8	6.8-19.3	1.8-11.6	8.0-11.7
Average maximal flow response to exercise	21.7	18.1	9.1	13.6
Range of response flow	13.6-34.2	11.2-25.4	2.5-15.2	10.2-16.5

TABLE 2.—*Estimation of Blood Flow to Skin and Muscle (Average for Each Group in ml./100 ml. Tissue/min.)*

	Young adults	Elderly adults	Elderly adults with obliterative arteriosclerosis	Arteriosclerosis after sympathectomy
Total number of cases	7	7	4	4
Basal blood flow	14.4	10.2	5.2	7.7
Response to exercise	22.4	13.5	7.4	9.9
Skin flow before exercise	6.5	6.0	2.7	4.4
Skin flow after exercise	9.8	6.3	3.8	5.6
Muscle flow before exercise	7.9	4.2	2.5	3.3
Muscle flow after exercise	12.6	7.2	3.6	4.3

METHODS AND MATERIAL

The response of peripheral blood flow to exercise was studied in 12 young healthy adults, 16 elderly persons without demonstrable vascular disease, 7 patients with nongangrenous obliterative arteriosclerosis, and 5 patients with nongangrenous obliterative arteriosclerosis in whom sympathectomy of a lower extremity had been performed. The blood flow to the lower extremity was measured plethysmographically. In corresponding smaller groups, skin flow and muscle flow had been estimated by means of individual skin mass/muscle mass ratios.[13] Surface temperature was recorded to ascertain "adaptation" to the environment. All experiments were performed in a constant-temperature room at 22 to 23 C. and 55 per cent humidity, with the subjects under basal conditions, and measurements were not begun until surface temperature remained constant for half an hour. After measurements of resting flow had been made, the subject exercised for 5 minutes by rhythmically pressing down on a footboard, adjusted within the plethysmograph casement, at a rate of 60 cycles down and up per minute; the completion of each cycle was indicated by a bell connected to the footboard. Recordings were made immediately after the exercise and every 2 minutes for 1 hour thereafter.

RESULTS

Under the experimental conditions described, basal flows were higher in young healthy adults than in the group of elderly persons without demonstrable vascular disease. They were lowest in patients with obliterative arteriosclerosis; sympathectomized limbs had a higher basal flow than the comparable nonsympathectomized ones. After exercise, there was an increase in total blood flow in all groups (table 1).

When "skin flow" and "muscle flow" were estimated separately in smaller groups (7 young adults, 7 elderly people, 4 arteriosclerotic and 4 sympathectomized patients), the figures listed in table 2 were obtained. Although the over-all increase after exercise was smaller in these subjects than in those reported in table 1, there was no difference in directional responses.

Statistical evaluation of the figures obtained in various groups yielded the following: 1. Although the blood flow in elderly people without vascular disease is persistently lower

han in young persons, the number of subects tested is not large enough to make the verage difference statistically significant. 2. Blood flow in patients with obliterative arerioscleroses is significantly lower than in oth (young and elderly) control groups ($p = .002$). 3. Resting blood flows in patients vith obliterative arteriosclerosis after sympahectomy are significantly higher than in nonympathectomized limbs ($p = .05$).

Conclusions

"Basal" flow figures corresponded to what might have been reasonably expected. Unfortunately, we do not have readings before and after sympathectomy in the cases reported here. All subjects who had been sympathectomized unilaterally had higher basal flow on the operated side than in the other limb.

It is of considerable interest that the apportioning of the total blood flow to the skin and muscle beds respectively shows the following trend. In the young healthy adults at rest, somewhat more blood goes to the muscles than to the skin; in elderly people without vascular disease the reverse is the case. Exercise increases muscle flow somewhat more than skin flow in these 2 groups. In patients with nongangrenous arteriosclerosis, the distribution is about equal. When sympathectomy has been performed, however, the skin obtains a greater share. The distribution is not significantly altered by the increase in total blood flow associated with exercise. In these experiments, sympathectomy did not seem to influence the over-all response to exercise. We know that vascular responses in the extremity to body warming are materially altered by sympathectomy. If we assume that our method of quantitating skin and muscle is correct, then we must conclude that the increase of blood flow in response to exercise is mediated by a mechanism different from that active in the Gibbon-Landis procedure.

Summario in Interlingua

Le cifras pro le fluxo "basal" correspond- a a lo que debeva esser expectate. Infelice- nte nos non ha lecturas ante e post sympathectomia in le casos hic reportate. Omne subjectos con sympathectomia unilateral habeva un plus alte fluxo basal al latere operate que in le extremitate intacte.

Il es de grande interesse que le apportionamento del total fluxo de sanguine al vasculaturas cutanee e muscular demonstra le sequente temdentias: In normal juvene adultos in stato de reposo, un pauco plus sanguine va al musculos que al pelle. In subjectos de etates plus avantiate sed sin morbo vascular, le contrario es ver. Exercitio augmenta le fluxo muscular un pauco plus que le fluxo cutanee in le mentionate 2 gruppos. In patientes con arteriosclerosis non-gangrenose, le distribution es quasi equal. Tamen, post sympathectomia le portion del pelle predomina. Le distribution non es alterate significativemente per le augmento del total fluxo de sanguine que es associate con exercitio. In iste experimentos, sympathectomia non pareva influentiar le responsa general a exercitio. Nos sape que responsas vascular evocate in le extremitates per calefaction del corpore es materialmente alterate per sympathectomia. Si nos suppone que nostre methodo de quantification pro pelle e musculo es correcte, nos debe concluder que le augmento del fluxo de sanguine in responsa a exercitio es mediate per un mechanismo que differe ab le mechanismo que es active in le procedimento de Gibbon-Landis.

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Vasomotor Responses to Cooling in the Extremities of Subjects with Neurologic Lesions

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Reflex vascular responses to cooling were studied in subjects with neurologic disorders, with a younger and an elderly "normal" group being used for comparison. By and large the responses were mirror images of those described for the Gibbon-Landis procedure. It was demonstrated that normal reflex responses to cooling as well as to warming are dependent upon the integrity of sympathetic innervation.

EVIDENCE of vasoconstriction in remote skin areas in response to local application of cold has been reported by various investigators.[1-6] Pickering[7] studied this response thoroughly; he showed that immersion of one hand and forearm in cold water produced a transient vasoconstriction of the opposite hand.

Two modes of action are probably involved in the reflex vasoconstrictor response to cooling an extremity, one transient due to afferent nerve stimulation, and one longer lasting due to the cooling of a body of blood which reaches the vasomotor centers.[5] This represents a Gibbon-Landis procedure with an opposite sign.[8] The reflex vasoconstriction is considered a measure of conserving body heat.[9]

Since the original work of Cannon and his co-workers,[10] altered responses to vasodilator stimuli in sympathectomized limbs have been the subject of several independent studies.[11-16] Lately, Redisch et al. were able to demonstrate that 7 of 11 sympathectomized lower limbs responded with a significant decrease in blood flow in response to a vasodilator stimulus (Gibbon-Landis procedure), while blood flow decreased as usual in the nonsympathectomized limb.[17] Goetz[11] also reported that, in some cases after sympathectomy, blood flow to the toe decreased in response to vasodilator stimuli. Prinzmetal and Wilson[12] showed that blood flow in the upper extremity decreased in response to the Gibbon-Landis procedure after sympathectomy in 2 patients with Raynaud's phenomenon.

Information is less complete as far as vasoconstrictor stimuli are concerned. Barcroft and Dornhorst[18] found a paradoxical response to cooling, namely, increase in blood flow in sympathectomized limbs. Ahmad[19] reported a patient, unilaterally sympathectomized for hyperhidrosis, who showed vasodilatation in the unsympathectomized hand in response to cooling the sympathectomized side. So far, this has remained an isolated observation. Goetz[11] reported an increase in pulse volume and rate of blood flow in completely sympathectomized lower extremities on cooling hands and forearm.

Hemiplegic limbs showed a delay of vasoconstrictor response to cooling, but no quantitative difference between the normal and hemiplegic sides. Uprus et al.[6] stated further that, in general, the functional capacity of hemiplegic limbs for vasoconstriction in response to a sensory stimulus or fall in blood temperature is unimpaired. Sturup and coworkers[5] arrived at the same conclusion and stressed that the reflex response to vasocon-

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strictor stimuli is completely independent of the continuity of anterior and posterior nerve roots, as long as the sympathetic nerve fibers remain intact.

The effects of transection of the spinal cord upon blood flow and vasomotor responses seem to be entirely dependent upon the level and completeness of the lesion. These 2 factors influence directly the degree of interruption of sympathetic pathways.[20] According to Pollock et al.[21] injury to the spinal cord renders the affected limb more sensitive to a decrease in environmental temperature as indicated by surface temperature readings. They attributed this to failure of the excitatory neural impulses to stimulate body heat production, due to interruption of suprasegmental reflex activity. Gilliat et al.[22] observed that in patients with cord lesions at T_4 or lower, vasoconstrictor reactions in the fingers occurred in response to cold and other stimuli to head or neck. Bumke and Foerster[23] were not able to elicit reflex vasoconstriction by stimulating cutaneous receptors below the level of the lesion. In case of midthoracic complete transection of the cord, they could produce vasoconstrictor responses in the arms by applying cutaneous stimuli well below the level of the lesion. Guttman and Whitteridge[24] could not confirm Foerster's observation: in their experiments, vasodilatation in response to visceral distention was mediated through fibers above the level of the lesion. The degree of disturbance in regulation of peripheral blood flow and other autonomous functions in complete spinal cord lesions increases in direct proportion to the height of the level of the lesion.

The following report deals with an attempt to determine more clearly the vascular reflex responses to cooling in subjects with neurologic lesions.

Methods and Material

All experiments were performed in a constant temperature room at 25 C. (± 0.5°) and 55 per cent humidity; thus, a mild vasodilator stimulus was applied against which the presumably vasoconstrictor reflex response to cooling was tested. The subject was in "basal" state clad in cotton pajamas, with the extremities exposed, and was considered "adapted" when the surface temperature of the plantar surface of the big toe had remained constant for at least ½ hour as recorded quasicontinuously on a Speedo-max surface temperature recorder. One upper extremity was then immersed in a water bath maintained at 15 C. for a period of 40 minutes. Vasomotor responses in the lower extremity were ascertained by periodic determination of the rate of blood flow measured with a large limb venous occlusion plethysmograph.[25] The following groups were compared: group 1, 5 young healthy adults; group 2, 6 elderly adults with demonstrable cardiovascular disease; group 3, 6 patients with peripheral occlusive arterial disease; group 4, 6 patients with hemiplegia; group 5, 7 patients with sympathectomy; group 6, 4 patients with transection of the spinal cord.

Results

Basal flows in young normal subjects were higher than in elderly subjects without demonstrable cardiovascular or neurologic lesions; the blood flow changes in response to a vasoconstrictor stimulus (cooling) showed the following trend: Peripheral blood flow decreased by an average of 40 per cent compared to the basal flow, in both groups; the maximal vasoconstrictor response in the young normal adults was reached at about 25 minutes after the cooling procedure was started; in contrast, in the elderly adults without demonstrable vascular disease, the maximum response was reached only after an average of 45 minutes, that is, shortly after the discontinuation of the cooling procedure. Surface temperature was decreased in most but not in all cases parallel with the plethysmographically measured blood flow. The small number of patients in each group precludes statistical evaluation. It is for this reason that the results for each patient are given.

Hemiplegic limbs showed a somewhat lesser basal flow than those of elderly subjects of the comparative age group without demonstrable arterial occlusive disease. Blood flow in the hemiplegic limbs decreased regularly but only slightly in response to the vasoconstrictor stimulus (cooling); changes remained within the range of 2 ml./100 ml. tissue/min. Comparison of hemiplegic limbs with limbs of patients with documented obliterative ar-

TABLE 1.—*Effects of Cooling Procedure on Blood Flow of the Lower Extremity (ml./100 ml. tissue/min.)*

Group 1 (young subjects)						Group 2 (elderly subjects)					
Patient	Age	Basal flow	Max. change	%	Time of max. response (min.)	Patient	Age	Basal flow	Max. change	%	Time of max. response (min.)
S.A.	23	12.3	— 4.0	32	15	K.E.	66	6.4	— 6.3	98	42
J.H.	26	28.6	—10.3	36	30	F.D.	58	9.9	— 4.0	41	60
J.J.	21	22.4	— 6.6	29	31	F.J.	57	10.3	— 4.0	38	30
A.M.	29	20.2	— 6.0	29	35	E.F.	54	6.6	— 3.4	51	45
J.P.	24	14.6	— 4.3	29	25	S.A.	62	8.6	— 2.0	23	40
Average		19.6	— 6.2	31	27	Average		8.3	— 3.9	46	43
Group 3 (hemiplegic patients)						**Group 4 (elderly patients with obliterative vascular disease)**					
W.E.*	63	2.6	— 1.0	38	40	W.B.	56	3.8	+ 0.9	23	45
P.E.*	49	4.6	— 1.9	41	45	L.F.	60	3.5	— 0.2	6	35
H.C.	44	5.3	— 0.5	9	40	B.M.	60	4.3	— 0.7	16	20
C.E.	60	8.0	— 2.0	25	30	McG.	58	7.9	— 0.4	5	40
M.R.*	58	3.2	— 0.2	6	30	C.H.	56	1.2	— 0.4	30	56
P.M.†	45	13.8	— 0.9	6	30	M.G.	52	1.2	— 0.5	41	35
Average		6.2	— 1.08	17	35	Average		3.6	— 0.4	11	38

*Patients with simultaneous obliterative arterial disease.
†Tested limb was previously sympathectomized.

TABLE 2.—*Effects of Cooling Procedure on Blood Flow of the Lower Extremity (ml./100 ml. tissue/min.)**

Sympathectomized limbs					
Patient	Age	Basal flow	Max. changes	%	Time of max. response (min.)
P.M.	45	16.3	+ 5.1	32	20
P.M.†	45	13.8	— 0.5	4	20
S.L.	56	6.4	+ 1.2	19	20
K.W.	60	5.1	+ 4.5	88	30
F.A.	55	5.9	+ 3.9	66	30
D.L.	54	2.7	+ 1.3	48	25
B.W.	56	7.3	+ 3.0	41	25
Average		7.2	+ 3.2	44	25
Range		2.7-16.3	—0.5–+5.1		

*Sympathectomy was performed because of obliterative arterial disease, except in P.M., who was operated on because of hypertension.
†Hemiplegic limb.

teriosclerosis revealed a similar fashion of vasomotor responses to cooling; the latter likewise showed only slight decrease in blood flow; their basal flows were, of course, lower than those of patients with hemiplegia.

Three of the 6 patients in the sympathectomized group had been operated upon for hypertension (lumbodorsal resection) and 3 for occlusive arterial disease (lumbar resection). Average basal flows were higher in limbs sympathectomized for vascular disease than in the comparable nonsympathectomized arteriosclerotic group (table 1). There was an average increase of 44 per cent in blood flow in response to the vasoconstrictor stimulus in all subjects, except in 1 patient whose sympathectomized limb was paralyzed: he showed no change in blood flow. One patient who had been sympathectomized for occlusive arterial disease on one side had small decrease in flow in the nonsympathectomized limb similar to the response of patients with obliterative arteriosclerosis in general.

In the sympathectomized group (table 2), the maximal blood flow responses were reached at an average of 25 minutes after cooling was started. Again, correlation between surface temperature and measured blood flow was poor.[17]

In the 4 paraplegic patients, the average basal flow was somewhat higher than in the patients with obliterative arteriosclerosis, but

TABLE 3.—*Influence of Cooling Procedure upon Blood Flow of the Lower Extremities in Paraplegic Patients (ml./100 ml. tissue/min.)*

Patient	Age	Basal flow	Max. changes	%	Time of max. response (min.)	Level of spinal cord lesion
N.V.	43	5.1	+12.3	241	20	Multiple sclerosis with spastic hemiplegia
H.W.	33	3.8	+ 5.3	139	60	C_7 - T_1 radiologically documented
G.M.	31	9.3	— 4.0	43	55	T_6 - T_8 radiologically documented
W.P.	29	8.8	— 1.6	18	73	Complete transection at T_{11} - T_{12} (fracture)

lower than in the 2 normal control groups (1 and 2). Reflex responses to cooling differed with the site and extent of the lesions. The first of the 4 subjects studied (table 3) and diagnosed as having multiple sclerosis with spastic paraplegia showed a marked increase in blood flow in response to cooling without any change in surface temperature. The second case with a radiologically documented transection at C_7-T_1 showed a 3-fold increase in blood flow in response to cooling of one upper extremity. Transections of the cord at the levels T_6-T_8 and T_{11}-T_{12}, respectively, were present in the 2 patients who showed diminution of blood flow similar to the response of the elderly "normal" group.

A graphic comparison of responses to cooling in the various groups tested is shown in figure 1. The small number of subjects in each group does not permit statistical evaluation. Changes within each group were, however, invariably in the same direction.

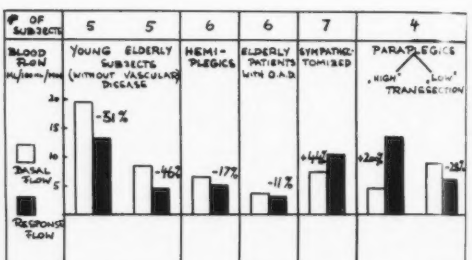

FIG. 1. Average blood flow changes in response to cooling.

DISCUSSION

Extremity blood flow in patients with various neurologic lesions and its behavior in the reflex response to a vasoconstrictor stimulus (cooling) reveal essentially "mirror images" of the vasomotor responses obtained by applying a vasodilator stimulus (warming). Lesions of the brain causing hemiplegia apparently do not interfere essentially with reflex responses to vasoconstrictor stimuli; it should be noted, though, that the decrease of blood flow in the hemiplegic limbs was smaller than in the comparable group of elderly subjects without neurologic or cardiovascular disorders. Three of the 6 hemiplegic patients have some degree of peripheral arterial occlusive disease, and their blood flows are therefore in general more nearly comparable to the group with obliterative vascular disease than do those without it.

The results obtained in the surgically sympathectomized group (increase in blood flow) were rather expected, since a "paradoxical" pattern in the reflex response to warming (decrease in flow) had been observed previous-

ly. The physiologic mechanism of such "reversal" of response to warming and cooling remains obscure and no satisfactory explanation can be offered so far. The same speculation as presented concerning reflex responses to warming[17] may be mentioned here: sympathectomy possibly alters an enzymatic process in the vessel wall that is most probably responsible for vasomotor activity, namely, the catecholamine-amine oxidase reaction.[26] It is unexplained why such alteration should become manifest only when a vasomotor stimulus (either vasodilator or vasoconstrictor) is applied. It may also be recalled again that Cannon and his co-workers[27, 28] have shown many years ago that denervation of an organ or part renders it more sensitive to epinephrine.

The reflex vasomotor responses to cooling in the paraplegic subjects were dependent on the level and completeness of their respective lesions similar to their previously reported reflex responses to warming. This corresponds to the accepted neurophysiologic concept, that sympathetic outflow to the lower extremities most probably starts at about the level of T_5-T_6.[29] In keeping with that concept, 2 paraplegic patients with documented lesions at T_6-T_8 and T_{11}-T_{12}, respectively, displayed "normal" reflex responses to cooling: their blood flow decreased. The 3-fold increase in blood flow in response to cooling, that was encountered in the paraplegic patient with multiple sclerosis and therefore undetermined locations of lesions, indicates, in all probability, an impairment of sympathetic pathways in the cord above T_5, since a subject with documented "high" transection exhibited the same response; blood flow in this limb increased almost 3-fold in response to cooling. It can be said that, by and large, patients with high transection of the cord (above T_5) behave in a manner quite similar to that of subjects after surgical sympathectomy.

Summary

Reflex vascular responses to a physiologic vasoconstrictor stimulus (cooling of one upper extremity) were ascertained in young healthy adults, elderly patients without demonstrable cardiovascular disease, hemiplegic patients, paraplegic patients, and subjects after surgical sympathectomy. Both young and elderly "normals" responded to cooling with a decrease in blood flow (reflex vasoconstriction). Hemiplegic patients (with arteriosclerosis) showed but small decrease in blood flow response to cooling similar to a control group of patients with obliterative arteriosclerosis. Basal blood flow was higher in the sympathectomized limbs and all of these subjects except 1 had an increase rather than decrease in blood flow in response to cooling; 1 did not show any change; none had a decrease. Paraplegic patients responded differently depending upon site and extent of their lesions; the ones with high transection of the cord showed a response similar to those seen after sympathectomy, while low transection did not alter the vasoconstrictor response to cooling. By and large, reflex responses to cooling are a "mirror image" of the reflex response to warming. Normal responses in both instances seem dependent solely upon the integrity of sympathetic pathways.

Summario in Interlingua

Le reflexe responsas vascular a un physiologic stimulo vasoconstrictori (frigidation de un del extremitates superior) esseva determinate in juvene adultos de normal stato de sanitate, in patientes de etate avantiate sin demonstrabile morbo cardiovaseular, in patientes hemiplegic, in patientes paraplegic, e in subjectos recentemente subjicite a sympathectomia chirurgic. Le subjectos normal—tanto juvene como etiam de etate plus avantiate—reageva al frigidation per un reduction del fluxo de sanguine (i.e. per vasoconstriction reflexe). Patientes hemiplegic con arteriosclerosis monstrava solmente un micre reduction del fluxo de sanguine in responsa al frigidation. In isto illes se comportava simile a un gruppo de controlo de patientes con arteriosclerosis oblitterative. Le fluxo de sanguine basal esseva plus alte in extremitates sympathectomisate, e omne le subjectos in iste categoria—con 1 exception—manifestava un aug-

mento plus tosto que un reduction del fluxo de sanguine in responsa al frigidation. In le caso exceptional, nulle alteration esseva notate. Casos de reduction non occurreva del toto. Le patientes paraplegic reageva diversemente secundo le sito e le extension de lor lesiones. In casos de transsection alte del corda, le responsa essea simile a illo vidite post sympathectomia, durante que transsection basse non alterava le responsa vasoconstrictori a frigidation. A generalmente parlar, le responsas reflexe a frigidation pare esser "imagines speculär" del responsas reflexe a calefaction. In ambe casos, le normalitate del responsas depende exclusivemente del integritate del vias sympathic.

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Pre-Harveian Doubts of Galenic Doctrine

The basic problem of both Galen and Servetus was how to move the blood from the right ventricle of the heart to the left. Galen had declared that the blood sweated through minute openings in the septum of the heart although there was some passage by anastomosis between the minute branchings of veins and arteries. Servetus announced that the transit occurred by a long course through the lungs although a very little blood, as he said, may pass through the septum of the heart. We may then say that there were two possible routes for the blood and that by the closing of the one, the other became essential, and already Vesalius in 1543 had cast some doubts on the passage through the septum of the heart although his complete denial of this route does not appear until 1555. Nevertheless, the doubt is there from 1543, and either in relation directly to Vesalius or through the influence of his book there must have been discussion on this point among physicians although they were still too timid to express their anti-Galenical stand in the permanence of print. In essence, Servetus without doing violence to the anatomical facts of Galen, "the traditional authority," simply made what might be called a quantitative reversal in the functions of the parts involved by stating that the bulk of the blood passed through the lungs from the pulmonary artery into the pulmonary vein, of course, by anastomosis between the veins and arteries described by Galen, while a very little, as Servetus said, might pass through the septum of the heart. It seems quite possible that Servetus did not actually believe in the permeability of the septum, but Galenical tradition caused him to refrain from a clear denial.—Charles D. O'Malley. *The Complementary Careers of Michael Servetus: Theologian and Physician.* History of Medicine and Allied Sciences **8**: 387, 1953.

Normal Response Curve to Exercise of Relative Cardiac Output Measured with Radioiodinated Serum Albumin

By Sylvan L. Weinberg, M.D., G. Richard Grove, Ph.D., Robert E. Zipf, M.D., David C. Daniels, B.S., and James P. Murphy, B.S.

A simple, relatively precise, and clinically applicable indirect method of determining relative cardiac output is presented. The principle involved is a modification of the dye-dilution principle and is performed by external monitoring of intravenously injected radioiodinated serum albumin combined with a standard detecting and recording device. This procedure was performed serially before and after a standard Master test, and the results in 19 healthy individuals describe a relative cardiac output exercise response curve for normal individuals. The utilization of cardiac output in the manner presented may add another clinical measurement of cardiac function.

ONE OF THE most challenging problems in clinical medicine is the delineation of boundaries of normal and pathologic cardiac states. In a cardiac survey a multilateral approach is employed including a history and physical examination, studies of the pulse, venous and arterial pressures, and respiration under various standardized circumstances. A battery of laboratory tests may include a blood count, serum lipid, and other blood chemistry determinations. In addition, circulation time, electrocardiograms, and appropriate x-ray and fluoroscopic studies are obtained. This standard diagnostic appraisal all too frequently fails to distinguish borderlines of disease. In many instances, by existing standards, the conclusion may be reached that the patient's responses are "within normal limits." Among these individuals, normal by criteria previously described, there must exist differences in cardiac function and possibly in disease not demonstrated by these clinical tests. In an effort to add another parameter of cardiac function to the battery of diagnostic methods, the clinical applicability of a cardiac output test in response to exercise with external monitoring of intravenously injected radioiodinated serum albumin (RISA) has been explored.

The values obtained by this technic are an indirect measurement but certainly a function of cardiac output. The exact relationship between the measured and the true values of cardiac output is not definitely known; however, because of the preciseness of this technic, relative changes in cardiac output in a given individual can be determined with great confidence even though the relationship to the absolute values is not accurately known. Thus, this technic has the potential of providing additional information on the relative changes of cardiac output with exercise that may be of value in the clinical assessment of cardiac function.

Methods and Materials

The method of determining cardiac output used in this study[1, 2] is a direct measurement of the mean residency time in the heart, which is probably related to cardiac output.[1,2] A predetermined amount of RISA was injected into the antecubital vein, and the radioactivity level over the heart was detected by a scintillation probe and recorded on a rectilinear-strip chart recorder. The dosage of RISA was 5 μc. for the first measure of cardiac output. The amount was doubled for each succeeding output in the series, making a total of 75 μc. for the 4 determinations. The probe was placed at an arbitrarily chosen point 4 cm. above and 2 cm. to the left of the inferior end of the sternum. A characteristic curve shows the radioactivity level observed over the heart during initial mixing and

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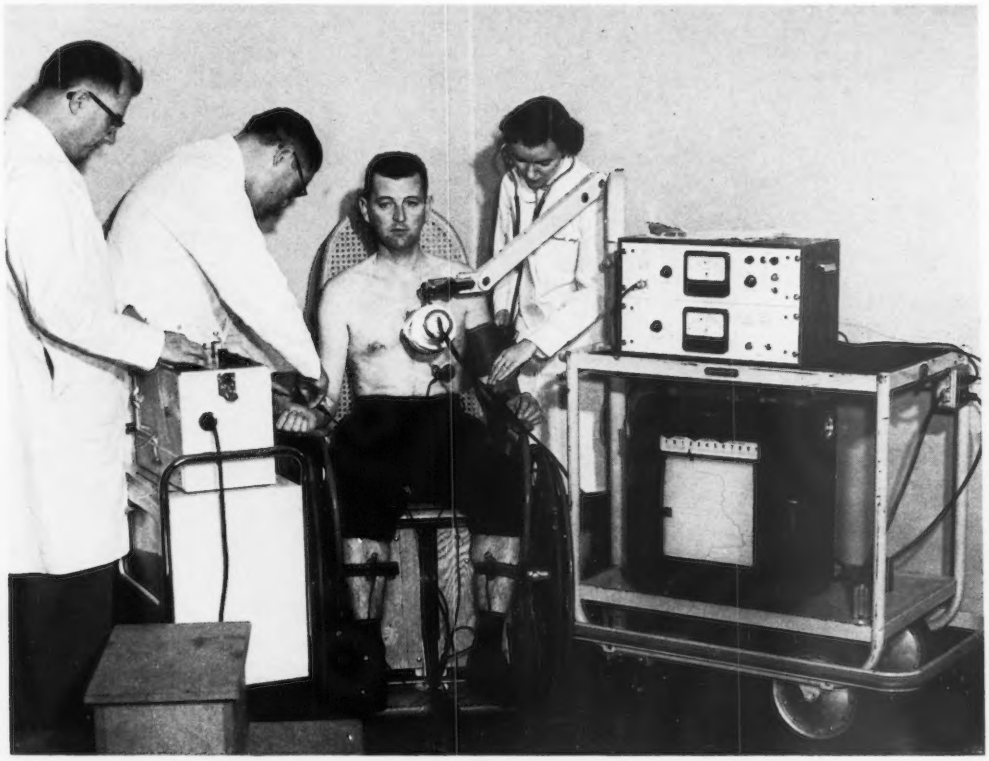

FIG. 1. Patient and equipment for obtaining physiologic data before and after Master 2-step test. The scintillation probe is in position over the heart and the strip-chart recorder is on the right.

its exponential diminution, which theoretically decreases to the original level for a single cycle through the heart and may be marked by a second rise due to recirculation of the radioactive material. The area under the curve was analyzed in sections by planimetry and calculated from formulas derived for this type of exponential response. The details of these calculations have been described.[1, 2]

This method of performing cardiac output was used in 19 healthy adult individuals in conjunction with the standard 2-step exercise test as described by Master and co-workers.[3] The series included 6 women, 22 to 32 years of age, and 13 men, 20 to 36 years of age. Each subject was seated comfortably in a chair (fig. 1). Resting baseline data included pulse, blood pressure, respiratory rate, electrocardiogram, blood volume done by a radioactive iodine technic,[4] and cardiac output. Ample time was allowed for the patient to relax, so that the data from the first cardiac output might be as basal as possible. The procedure was explained to the patient in advance to allay any anxiety that might arise from seeing the unfamiliar equipment. The patient performed a standard 2-step exercise test, which consisted of the appropriate number of trips in accordance with the patient's sex, age, and weight in 1.5 minutes. Immediately following the end of exercise the entire battery of physiologic observations was repeated. An effort was made to perform the cardiac output immediately after exercise was completed. Speed was facilitated by leaving an indwelling needle with obturator in the antecubital vein during the period of exercise. Electrodes were left in place with the leads attached so that the electrocardiogram could be taken simultaneously with the cardiac output following exercise. Observations were repeated at 4.5 and 8 minutes after exercise.

RESULTS

There were no unusual changes in the pulse rate, blood pressure, or respiratory rate in the 19 cases. The series of 4 electrocardio-

TABLE 1.—*Pulse Rate and Cardiac Output before and after Exercise*

Subject no.	Sex	Age	Ht.	Wt.	Blood volume (ml.)	Before exercise		After exercise: Immediately		After exercise: 4.5 minutes		After exercise: 8 minutes	
						Pulse	Cardiac output (L./min.)	Pulse	Cardiac output (L./min.)	Pulse	Cardiac output (L./min.)	Pulse	Cardiac output (L./min.)
1	M	21	6′	175	6355	70	6.85	84	11.45	70	7.38	70	5.77
2	M	34	5′11″	168	5732	84	5.49	112	12.00	84	6.94	76	5.45
3	M	24	5′5″	128	4534	88	6.56	112	9.50	80	6.02	80	6.49
4	M	22	6′	172	7198	76	10.20	88	15.35	76	13.99	72	9.18
5	M	36	5′9″	172	4856	80	5.96	96	8.97	76	7.46	80	4.55
6	M	30	5′10″	185	5291	68	7.55	96	10.96	64	8.99	68	7.85
7	M	22	6′2″	182	6319	96	9.94	120	14.84	104	8.53	98	8.57
8	M	24	6′	167	5671	75	8.00	75	15.13	75	12.50	76	6.02
9	M	20	5′6″	140	4274	72	5.78	108	10.33	85	6.17	84	4.40
10	M	22	5′10″	140	6189	72	11.42	96	—	72	10.16	72	7.17
11	M	21	5′10″	175	6616	76	5.46	80	9.33	76	8.46	76	—
12	M	20	5′10″	170	6417	84	5.07	116	13.60	88	8.28	88	9.28
13	M	31	5′9″	145	4634	80	6.56	100	8.35	76	5.68	80	5.47
14	F	22	5′5″	128	4187	100	7.54	120	13.24	90	8.38	100	6.98
15	F	32	5′4″	106	3915	80	5.46	92	8.70	80	5.29	92	5.40
16	F	32	5′4″	115	3960	100	11.70	116	14.06	100	9.00	100	7.71
17	F	20	5′9″	140	4067	100	—	120	10.70	100	7.25	96	6.59
18	F	27	5′3″	116	3644	100	7.40	108	11.92	100	10.54	100	7.72
19	F	22	5′6″	129	4221	96	5.29	120	11.21	92	7.23	84	7.55

grams for each patient in no instance revealed a positive exercise test. The data for cardiac output for each case and the averages are shown in table 1. While minor discrepancies occur in some instances a consistent pattern is apparent with the cardiac output rising sharply after exercise in the order of 1.5 to 2 times the resting level. At 4.5 minutes the cardiac output in most instances returned approximately to control levels and in nearly every instance the output recorded 8 minutes after exercise was below the resting level. The results plotted in figure 2 show data considered to be a normal cardiac output response curve following the exercise burden imposed by the Master test.

DISCUSSION

The heart's function as a pump is to maintain an adequate blood flow to the tissues of the body. To provide appropriate increases in blood flow in response to specific demands is an equally important function of the pump. The importance of cardiac output in physiologic and disease states has been recognized for many years. Since the introduction of dilution technics for determining cardiac output by Stewart[5-7] and their modifications by Hamilton and co-workers,[8-10] the need for simplification of methods to permit wider clinical application has been apparent. Rushmer[11] has emphasized the potential clinical importance of a practical means of measuring cardiac output in response to a work load in the diagnosis and prognosis of heart disease. At the present time, however, measurement of cardiac output and its response to exercise has not achieved full clinical usefulness. In order for a measure of cardiac output to be applicable clinically, certain criteria must be met. These might include accuracy, reproducibility, safety, convenience, capability of serial repetition, and noninterference with therapeutic or diagnostic activities. The experiments reported here suggest that externally monitored RISA as used in this series of patients fulfills the criteria of clinical applicability. Data for reproducibility and internal precision have been previously documented,[1, 2] indicating a 50 per cent probable error of 17.5 per cent in 98 cases and an average probable error of 6.1 per cent in 3 serial determinations in the same patient for a series of 20 individuals.

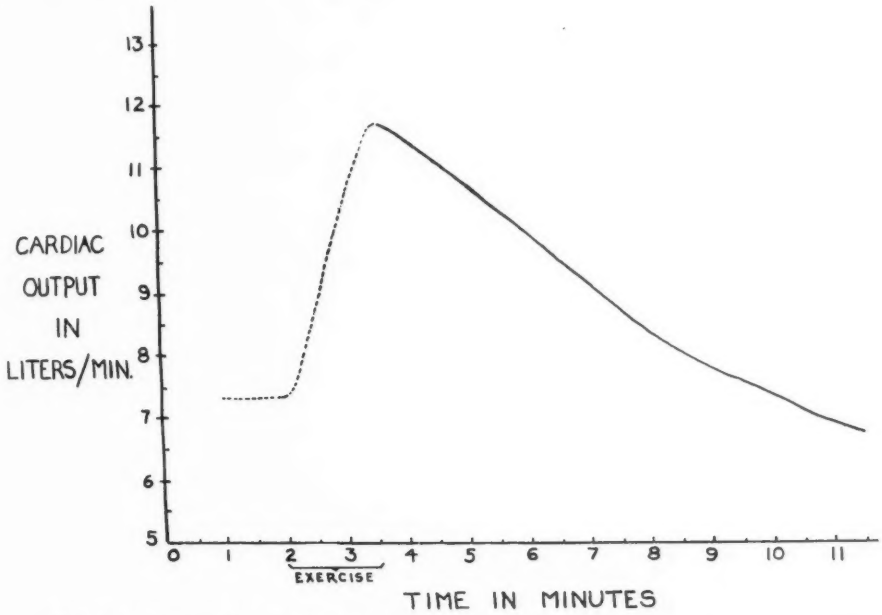

FIG. 2. Average cardiac output data from 19 normal patients showing the output response following the standard Master test in relation to time. The average cardiac output in liters per minute is 7.35 resting, 11.65 immediately postexercise, and 8.33 and 6.79 at 4.5 and 8 minutes postexercise, respectively. There is a 50 per cent probable error of 17.5 per cent.

The internal precision is particularly pertinent in situations where repeated observations are made in the same patient for a comparison of varying physiologic states. The cardiac output with externally monitored RISA inflicts no trauma to the patient other than that of a venipuncture. It can be done at the bedside with the patient in a recumbent or sitting attitude. It may be repeated at any interval of time from several minutes to greatly extended periods of time depending on the nature of the physiologic problem being observed. With regard to safety, the amount of radioactive exposure must be considered. A series of 4 cardiac output determinations done in approximately 12 minutes utilizes a total of 75 μc. While no absolute data for radiation tolerance can be defined at this time, the radioactivity involved is minimal by present standards. It is considerably less than that used in other methods recorded for estimating cardiac output by isotope techniques.[12-14] Although the amounts of radioactive materials used in this technic are considerably less than other technics described, the cardiac output is relative and its precise relation to outputs measured by other methods has not been determined.

In the series of patients presented, serial cardiac output determinations are correlated with the Master 2-step test. The Master test has been evaluated recently by Ford and Hellerstein,[15] who found it to be sound physiologically in that it imposes a similar energy demand on individuals of different age and weight. They emphasized the failure of patients with heart disease to increase oxygen utilization normally during exercise. They speculated that this might be due either to a failure to increase cardiac output in response to exercise or to a reduced arteriovenous oxygen difference, probably the former. The data presented here indicate that a predictable change in cardiac output does, in fact, occur in response to the exercise load of the Master test in normal patients. The changes in car-

diac output follow a pattern that might be termed the normal cardiac output response curve. It would appear that measurement of the cardiac output in response to the Master test may be a valuable supplement to the other data obtained in conjunction with the Master test, such as pulse, blood pressure, electrocardiogram, and oxygen consumption. The cardiac output response curve may form a standard by which abnormal functions of the heart may be detected where other parameters are within normal range. Preliminary data show variations from the normal cardiac output response curve in various disease states such as arteriosclerotic, valvular, and congenital heart disease.

Summary

The clinical applicability of this method of performing cardiac output by means of externally monitored radioiodinated serum albumin has been demonstrated. Serial cardiac output determinations have defined a normal cardiac output curve in response to the load imposed by the Master test in normal patients. The potential usefulness of the cardiac output response curve is suggested as a valuable supplement to the physiologic data obtained in conjunction with the Master test in defining boundaries of normal and disordered cardiac function.

Acknowledgment

Acknowledgment is made to Richard T. Light, Lenora Ralston, Phyllis L. Dinkel, and Mrs. Flo Ella Phillips for their invaluable technical assistance.

Summario in Interlingua

Es demonstrate le applicabilitate clinic del methodo de determinar le rendimento cardiac per sequer al extero le radioactivitate de iodo^{131} in albumina seral. Determinationes serial del rendimento cardiac ha resultate in le definition de normal curvas de responsa del rendimento cardiac sub le effecto del carga imponite per le test de Master in subjectos normal. Es suggerite que le curva del responsa del rendimento cardiac es de valor como supplemento al datos physiologic obtenite in conjunction con le test de Master pro definir le limites inter normalitate functional e dysfunction del corde.

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A Study of Cases Manifesting Low Voltage in the Frontal Plane Electrocardiographic Leads

By Richard W. Watts, M.D., and Kemal Gursal, M.D.

A study of 20 consecutive examples of frontal plane electrocardiographic low voltage revealed an incidence of 2.1 per cent among 935 patients having electrocardiograms. Arteriosclerotic heart disease was the most common cause and carried a high mortality rate. The striking lack of correlation between low voltage and heart size was pointed out and reasons for it are discussed. The lack of added value that the criteria of low voltage in the precordial leads afforded is also discussed.

TRADITIONAL teaching concerning frontal plane electrocardiographic low voltage has included myxedema, chronic constrictive pericarditis, pericardial effusion, and Addison's disease.[1] Myocardial fibrosis,[2] myocardial atrophy,[3] and endocardial fibroelastosis[4] have also been found to cause low voltage. To discover the causes and relative frequencies of these or other diagnoses in a general hospital the following survey was undertaken. Low voltage was defined as showing less than a 5 mm. QRS in all standard and unipolar limb leads. The precordial leads, as will be explained later, were not considered in the determination of low voltage.

To obtain the 20 cases herein reported 1,756 consecutive electrocardiograms on 935 patients in a 6-month period were examined. Thus low voltage occurred in 2.1 per cent of these patients. Table 1 lists the pertinent data on these patients. Notable was the high average age (63 years), the predominance of males (65 per cent), and the high death rate (50 per cent). Evidence of congestive failure was present in 8 patients, all but 1 of whom died. Hypertension was present in 4 patients. Three had hyperglycemia and 4 had elevation of blood urea nitrogen; all of these patients died. Serum cholesterol was not elevated in any. Chest x-rays showed cardiac dilatation in patients. Electrocardiographic diagnoses in addition to low voltage included myocardial infarcts in 6, right bundle-branch block in 3 (1 with myocardial infarct), left bundle-branch block in 1, atrial fibrillation in 5, and first-degree atrioventricular block in 1 case. Illustrations of some of the electrocardiograms are included (figs. 1-4).

Final diagnoses showed arteriosclerotic heart disease in 11 patients, 8 of whom died. There were no cases of myxedema, chronic constrictive pericarditis, pericardial effusion, Addison's disease, or endocardial fibroelastosis. One case of malignant disease (melanoma of the eye with metastasis to the liver) occurred. Three patients had no evident cause for low voltage. They were all women and their initial diagnoses included menorrhagia, reactive depression, and fever of unknown origin.

Autopsy data, listed in table 2, showed heavier than normal hearts in 3 of the 4 autopsied cases. Weinstein et al.[2] also made a similar observation. They attributed the fibrosis and low voltage to left ventricular hypertrophy rather than to coronary artery disease in some instances. They also found a lack of correlation between heart weight and low voltage (including precordial lead criteria) in that only 3 of 28 cases with low voltage had abnormally small hearts while 1 heart weighed 1,250 Gm. Correlation of low voltage with thickness of the left ventricular wall in Weinstein's data was somewhat more accurate in that 7 of the hearts had left ventricular walls less than 12 mm. thick, but 4 had walls more than 18 mm. thick. It is evident therefore that heart weight and thickness of the left ventricular wall have very

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TABLE 1.—*Data on Twenty Patients with Frontal Plane Low Voltage*

Case no.	Age, sex	Blood pressure	Congestive failure	Heart size by x-ray	Electrocardiogram	Diagnosis	Outcome
Arteriosclerotic heart disease							
1	69M	140/ 80	+	Large	Right bundle-branch block	Bronchopneumonia	Alive. Arteriosclerotic heart disease; cerebral vascular accident
2	65M	140/ 80		Normal	Left bundle-branch block	Silicosis	Alive. Arteriosclerotic heart disease
3	61M	140/ 98			Post. myocardial infaret	Arteriosclerotic heart disease	Alive
4	59M	190/110	+		Anteroseptal myocardial infaret	Arteriosclerotic heart disease	Died, no autopsy
5	57M	145/105	+		Atrial fibrillation	Arteriosclerotic heart disease	Died, no autopsy
6	82M	105/ 70	+		Atrial fibrillation; anterior myocardial infaret	Uremia	Died, no autopsy
7	70M	195/115			Atrial fibrillation; Right bundle-branch block	Cerebral vascular accident; diabetes	Died, no autopsy
8	81M	140/100	+			Hematemesis	Died, no autopsy
9	50M	115/ 90	+	Large	Right bundle-branch block; anterior myocardial infaret	Arteriosclerotic heart disease	Died, autopsy done
10	67F	150/100	+	Large	Anteroseptal myocardial infaret; atrial fibrillation	Diabetes	Died, autopsy done
11	65F	130/ 80	+		Atrial fibrillation; lateral myocardial infaret	Arteriosclerotic heart disease	Died, no autopsy
Other cause							
12	54M	150/ 90		Large	Right bundle-branch block	Rheumatoid arthritis	Alive
13	49F	132/ 80		Normal		Rheumatoid arthritis; nephritis	Alive
14	69M	150/ 60				Pyelonephritis	Died, autopsy done
15	73F	110/ 64		Normal		Fractured femur	Alive
16	71M	135/ 86		Normal		Parkinsonism	Alive
17	66M	160/100			Atrial fibrillation	Melanoma	Died, autopsy done
Unknown							
18	57F	155/100		Normal		Fever of unknown origin	Alive
19	54F	140/ 70		Normal		Depression	Alive
20	46F	145/ 83				Menorrhagia	Alive

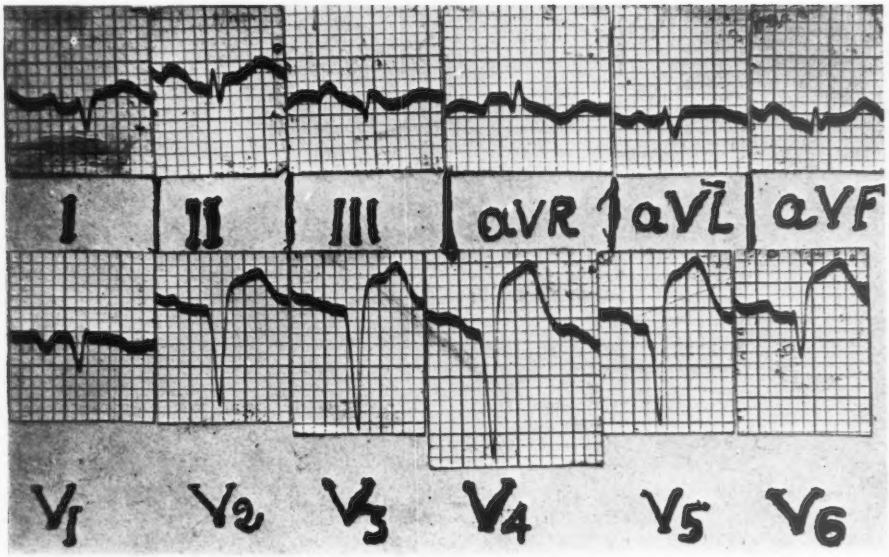

FIG. 1. Case 4, a 59-year-old man with anteroseptal myocardial infarct and frontal plane low voltage.

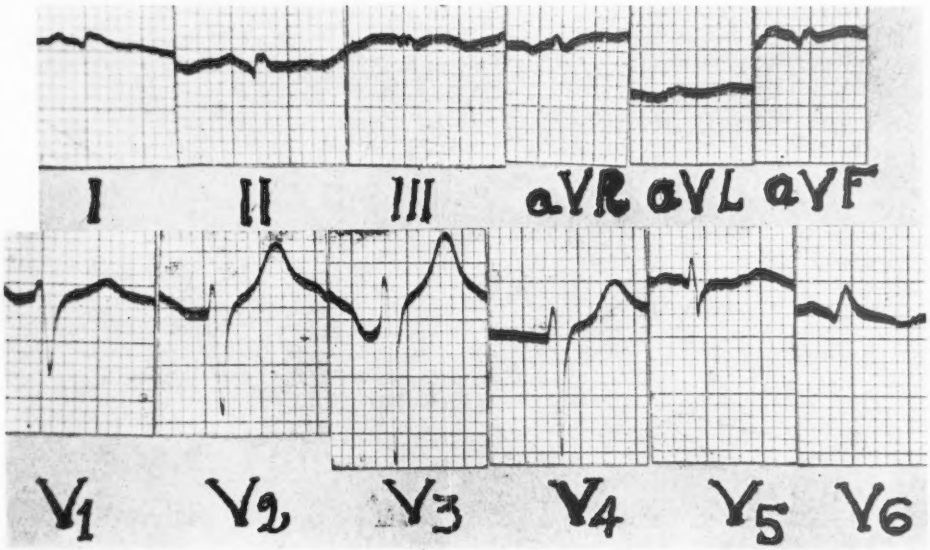

FIG. 2. Case 8, an 81-year-old man with arteriosclerotic heart disease but no definite myocardial infarct. Voltage is markedly low in the frontal plane but normal in leads V_2 to V_4.

ttle relationship to low voltage. A similar ck of correlation between anatomically roved atrophic hearts and electrocardiographic low voltage was shown by Hellerstein al.[3]; in their study only 56 per cent of such earts showed low voltage.

Electric functional integrity, or lack of it, is much more important in the generation of voltage in the electrocardiogram. The correlation of hypertrophy with high voltage is good although not complete.[5] The effect of myocardial fibrosis which, while adding to the

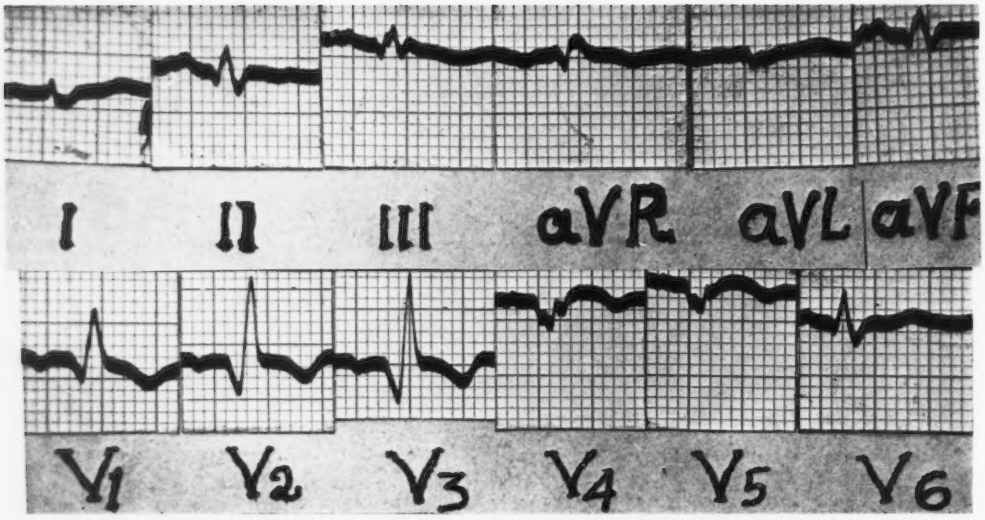

FIG. 3. Case 9, a 50-year-old man with anteroseptal myocardial infarct and right bundle-branch block. The heart weight was 440 Gm.

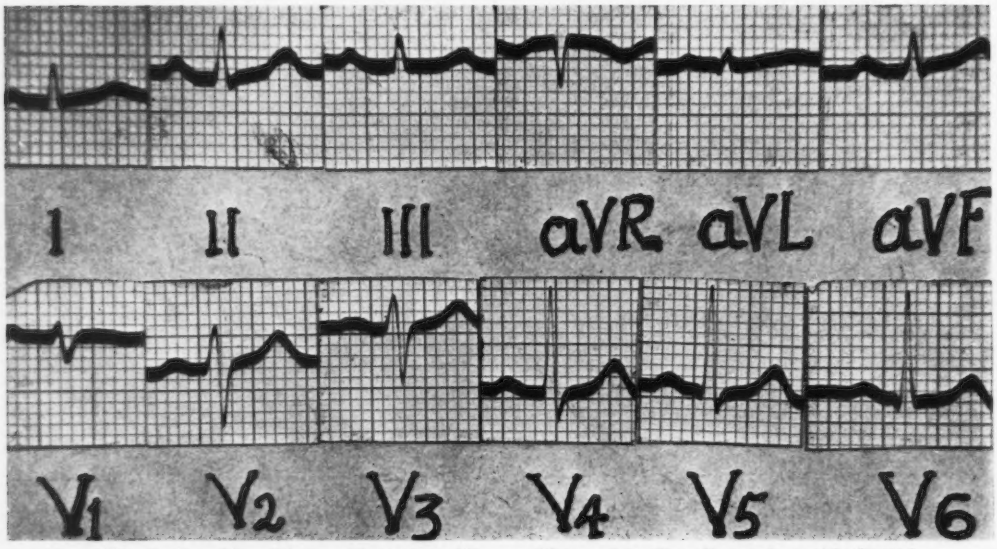

FIG. 4. Case 19, a 54-year-old woman with no evidence of cardiac disease but with frontal plane low voltage.

heart weight subtracts from the electric activity, may help to explain the poor correlation. Furthermore, the effect of fibrosis may explain the puzzling cases of unexplained abnormally large hearts having only coronary arteriosclerosis.

We did not use the criteria of low voltage in the precordial lead (less than 10 mm. in any V lead except V_1) in our selection of cases, and indeed none of our cases showed such low voltage in all the precordial leads. Studies by Lapin,[6] who used such criteria,

TABLE 2.—*Autopsy Data in Four Cases*

Case no.	Weight of heart (Gm.)	Diagnoses
10	360	Infarct of anterior wall, apex, and septum of left ventricle; also posterior wall with mural thrombus; generalized arteriosclerosis; hydrothorax, bilateral; recent infarcts of spleen and left kidney; chronic cholecystitis and cholelithiasis
14	540	Acute and chronic pyelonephritis; benign hyperplasia of prostate; bronchopneumonia; generalized arteriosclerosis
17	320	Melanoma of right eye with metastases to liver; generalized arteriosclerosis
9	440	Infarct of anterior wall of left ventricle, mural thrombus; hydrothorax; ascites; recent infarct, lower lobe of right lung

seemed to us to offer no additional advantage. Indeed Lapin found only 3 cases in which low voltage existed in any of the precordial leads. In 29 of the instances the RS voltage was over 20 mm. in another precordial lead, thus indicating that low voltage was due to myocardial infarct or shift of electric axis for other reason. However, comparison of his cases with frontal plane low voltage alone to those with additional precordial low voltage disclosed almost exactly the same type of cases as ours, in that 75 per cent and 77 per cent respectively had arteriosclerotic heart disease. We therefore consider that the additional criteria of precordial low voltage serve no useful purpose.

CONCLUSIONS

Twenty consecutive cases of low voltage in the frontal plane electrocardiographic lead, an incidence of 2.1 per cent of patients having electrocardiograms, are reviewed.

The high incidence of arteriosclerotic heart disease (55 per cent) and its high mortality rate (73 per cent) are contrasted to the lack of some of the more commonly considered causes of low voltage.

The striking lack of correlation between low voltage and heart weight or thickness of the left ventricular wall is emphasized.

The lack of additional value in the use of the criteria of low voltage in the precordial lead is pointed out.

SUMMARIO IN INTERLINGUA

Es presentate un revista de 20 casos consecutive de basse voltage in le derivationes electrocardiographic del plano frontal. Con respecto al serie total in que le 20 casos esseva trovate, illos representava un incidentia de 2,1 pro cento.

Le alte incidentia de arteriosclerotic morbo cardiac (55 pro cento) e le grande mortalitate inter le casos de ille morbo (73 pro cento) forma un contrasto acute con le absentia de certe altere, communmente considerate causas de basse voltage.

Es sublineate le frappante absentia de ulle correlation inter basse voltages e pesos de corde o spissitates del pariete sinistro-ventricular.

Es signalate le manco de valor additional del uso del criterio de basse voltage in derivationes precordial.

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Osmole and Water Excretion in Mercurial Diuresis in Congestive Heart Failure

By Norton Spritz, M.D., George W. Frimpter, M.D., Warren S. Braveman, M.D., and Albert L. Rubin, M.D.

The relationhip between water and total solute excretion following mercurial administration has been previously studied in normal human subjects during superimposed water and solute diureses. It is the purpose of the study to determine the solute/water relationships in the mercurial diuresis produced in water-deprived patients with edema from congestive heart failure. The results indicate that in such patients, the diuresis produced has the relationship of a simple osmotic diuresis. The clinical implications are discussed.

IN EXPERIMENTS on normal human subjects and laboratory animals, the variations in the concentration of urine solutes have been described during osmotic diuresis.[1-8] The present concept of the mechanism for the production of urine of greater solute concentration than plasma has been defined by Smith and associates[2, 4, 7] and reviewed by Welt[9, 10] and is based on measurements of solute excretion (expressed as osmolal clearance) and the relationship of this excretion to the rate of urine flow during such diureses. The resulting concept is that of a fixed and maximal removal of solute-free water from the distal tubular fluid to produce a concentrated urine in the setting of maximal antidiuretic hormone (ADH) activity.

It has been shown that the mercurial diuresis of normal subjects when superimposed on an osmotic or water diuresis satisfies this principle of a relatively fixed and maximal free water reabsorption.[6, 7] The finding by Grossman and co-workers[11] of a phasic variation in free water reabsorption during mercurial diuresis in normal subjects receiving pitressin, and the observation by Ladd[6] of a decrease in free water excretion during water diuresis after mercaptomerin may indicate, however, that in a diuresis due only to mercurials, solute and water relationships characteristic of simple osmotic diuresis may not obtain.

It is the purpose of the present study to report the patterns of solute and water excretion in mercurial diuresis in patients with congestive heart failure, and to relate these findings to those obtained in normal human subjects in the above experiments. It is hoped that such data will permit estimations of the relationship between fluid and solute loss during such diureses in the clinical setting.

Method

Seven men with congestive heart failure were selected for study. All had an elevated venous pressure, cardiomegaly, and edema at the time of the experiment. All were receiving maintenance doses of digitalis and none had received any diuretic for at least 72 hours prior to the study. There had been no oral or parenteral intake for at least 12 hours prior to the study.

An indwelling Foley catheter was inserted and urine collections were made with bladder compression, without irrigation, at intervals of 15 to 2 minutes. Venous blood was obtained without stasis at the time of each urine collection in 2 patients and at 1- to 2-hour intervals in the other patients. The subjects were recumbent throughout the study.

Urine volume, flow rate (V), and urine osmolality were determined on each specimen, the latter by means of a Fiske Osmometer (freezing point). Total solute excretion (UosmV), osmolal clearance (Cosm = UosmV/Posm), and free water reabsorption ($T^{c}_{H_2O}$ = Cosm-V) were calculated. In 5 patients the endogenous creatinine clearance (Creat

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TABLE 1.—*Statistical Relations between Urine Flow-Rate and Osmolal Clearance*

Patient no.	Posm range	Uosm range	Urine flow range (ml./min.)	Cosm range ml./min.	Correlation coefficient	Regression coefficient* (slope)	Remarks
1	297-295	412-297	.98- 7.0	.83- 6.63	.96	1.00	Merc. 2 ml. i.v.
2	305-299	QNS-346	<.1- 7.35	QNS- 8.49	.99	1.05	Merc. 2 ml. i.m.
3	288-283	730-318	.67-16.45	1.68-19.43	.95	1.11	Merc. 2 ml. i.m. Pit. 100 mu. i.v.†
4	292-291	800-313	.54- 4.64	1.49- 5.56	.88	.94	Merc. 2 ml. i.m.
5	295-287	870-376	.52- 8.47	1.62-11.17	.99	1.09	Merc. 2 ml. i.v. Pit. 700 mu. i.v.‡
6	295-285	485-321	1.00-10.33	2.27-11.53	.97	.92	Merc. 2 ml. i.m.
7	276-272	670-370	1.25- 9.08	3.07-11.00	.87	.98	Merc. 2 ml. i.m. Pit. 200 mu. i.v.†

*Mean 6, 1.01 ± .07.
†Administered after mercurial effect.
‡Begun prior to mercurial administration.

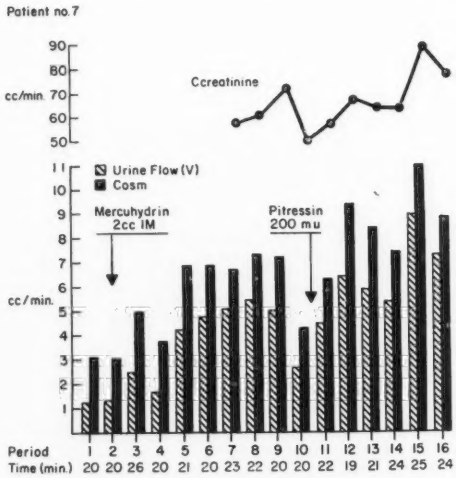

FIG. 1. Graphic presentation of the data obtained during 16 study periods in patient 7. $T_{H_2O}^{C}$ is represented by the difference between osmolal clearance (*solid bar*) and urine flow rate (*hatched bar*).

was determined for each period following mercurial administration during which the rate of urine flow exceeded 2 ml. Creatinine determinations were done by the sodium hydroxide-picric acid method of Bonsnes and Taussky.[12]

Meralluride (70 mg.) was administered as Mercuhydrin 2 ml. intramuscularly or intravenously after 2 or more control periods. Pitressin was given to 3 patients: 1 received 100 milliunits (mu.) intravenously during the control period and then 100 mu./hr. throughout the study; the other 2 received 100 mu. intravenously in a single dose after the mercurial effect had been established.

RESULTS

Table 1 is a compilation of the data obtained in the 7 patients studied. Figure 1 shows graphically the results obtained throughout the experiment in patient 7.

Urine Flow. In all patients there was a diuretic response to mercuhydrin. Maximum urine flows were 4.64 to 16.45 ml./min. The urine flow during the control period was less than 1.25 ml./min. in all subjects. This rate of urine flow after mercurial administration compares to 4.2 to 18.5 ml./min. obtained in normal subjects given mercurial diuretic while receiving large amounts of pitressin.[11]

The response to mercurial did not have symmetrical ascending and descending limbs, but rather was irregular, often with a period of maximal response immediately following a period only slightly greater than the control (fig. 1).

Endogenous creatinine clearance, measured after the establishment of mercurial effect, correlated significantly with variations in urine flow rate (table 2).

Urine Osmolality. The control urine osmolality varied from 412 to 870 mM/Kg. in the 7 patients studied, indicating varying degrees of impairment of concentrating ability.[13] Following mercurial diuresis, urine osmolality fell in every instance toward that of plasma. There was a significant inverse relationship

TABLE 2.—*Statistical Relation between Endogenous Creatinine Clearance and Urine Flow Rate in Four Patients*

Patient	C creatinine range (ml./min.)	Urine flow range (ml./min.)	Correlation coefficient	No. of periods	p
4	21-46	.53- 4.64	.89	11	<.01
5	72-97	.52- 8.47	.95	7	<.01
3	79-120	.67-16.45	.72	16	<.01
7	51-90	1.25- 9.08	.88	12	<.01

The clearance was determined for each period during which the urine flow rate exceeded 2 ml./min.

between the rate of urine flow and osmolal concentration in all patients ($p = .03$).

Plasma Osmolality. During the control period plasma osmolality ranged from 276 to 305 mM/L. in the 7 subjects. Normal range in this laboratory is 285 ± 8 mM/L. In each patient there was a decrease in plasma osmolality during the diuresis, with a maximum decrease of 10 and a mean of 5.1. The decrease in 5 of the patients exceeded 2 mM/L., which is the maximum attributable to laboratory error.

Osmolal Clearance. The osmolal clearance during control periods ranged from .83 to 3.07 ml./min. in the 6 patients with control urine flows great enough to allow this measurement. The maximum osmolal clearance ranged from 5.56 to 19.43 ml./min. in the 7 patients studied.

Figure 2 indicates the graphic relationship between osmolal clearance and urine flow rate for each of the patients. The slopes varied from y = .92 to 1.11 with a mean of 1.01 ± .07. This figure does not vary significantly from 1.00 and indicates a relatively fixed free water reabsorption. This finding compares with a mean slope of 1.03 ± .07 obtained by Smith[4] in normal subjects undergoing a mannitol osmotic diuresis.

Free Water Reabsorption ($T^c_{H_2O}$). In the 7 subjects studied, the $T^c_{H_2O}$ varied from 0.33 to 2.6 ml./min. This finding again indicates renal tubular functional impairment, since $T^c_{H_2O}$ is reported to be between 4 to 6 ml./min. per 1.73 M.² body surface in studies on normal hydropenic subjects.[4, 9, 11] Since these measurements were not repeated after compensation, the role of heart failure in this observed decrease cannot be stated.

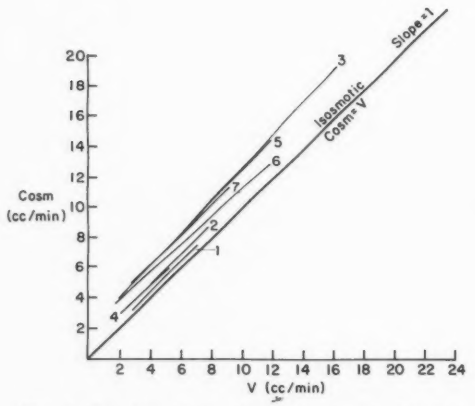

FIG. 2. Graphic relationship between osmolal clearance and urine flow rate in the 7 subjects studied. Solute-free water reabsorption is represented by the difference between the curve obtained and the isosmotic parameter. Periods during which the rate of urine flow exceeded the mean free water reabsorption were used. The *numbers* refer to individual patients (table 1).

The variations in $T^c_{H_2O}$ noted in each patient were related neither to changes in the rate of urine flow nor to variations in osmolal clearance. These changes were also shown to have no relationship to changes in plasma osmolality in the 2 subjects in whom this was determined for each urine collection period.

In 4 patients, in whom creatinine clearance was determined after mercurial administration for each period during which urine flow rate exceeded 2 ml./min., the correlation coefficient between this measurement and free water reabsorption ranged from 0.57 to 0.86, a statistically significant correlation in the 3 patients with more than 10 study periods (table 3).

Effect of Pitressin. Pitressin administered to 1 patient during the control period produced no change in the urine flow rate of 0.52 ml./min., and urine osmolality changed only from 876 to 880 mM/L. This would indicate maximal antidiuretic hormone activity at the

time of the study. This finding is consistent with the results of previous studies in patients with congestive heart failure.[14] Continuation of intravenous pitressin administration throughout the ensuing mercurial diuresis did not prevent the subsequent decrease in urine osmolality during periods of higher flow rate, nor did it influence the relationship between flow rate and osmolal clearance in this patient (fig. 2, patient 5).

In 2 patients (nos. 3 and 7), pitressin was administered as 1 intravenous injection after the establishment of mercurial effect. The mean free water reabsorption in the periods prior to pitressin injection was 2.11 ml./min. and was 2.22 ml./min. in the subsequent periods in one patient and 2.10 and 2.14 respectively in the other. These differences are not significant, and this again suggests maximal antidiuretic hormone effect throughout the period of this experiment.

Discussion

The results of this study indicate that the mercurial diuresis in patients with congestive heart failure has the same water-to-solute relationship as osmotic diuresis in normal subjects and experimental animals.

Since the free water reabsorption is relatively constant and not related to the rate of urine flow, the amount of solute excreted in a given urine volume will depend upon 2 factors under the conditions of this experiment. The first of these is the capacity of the individual patient for free water reabsorption at the time of diuresis. It is evident that a patient with marked impairment of free water reabsorption will have a diuresis essentially isotonic with plasma after the administration of mercurials, no matter what urine flow rates are attained. The second factor that will determine water-to-solute relationships in a mercurial diuresis is the rapidity with which a given volume is excreted. Since free water reabsorption is relatively fixed, the osmolality of the urine during lower flow rates will be greater. A prolonged diuresis of moderate flow rate will therefore result in the loss of more solute per given urine volume than would a diuresis of the same volume that resulted from a greater urine flow rate for a shorter period.

Table 3.—*Statistical Relationship between Endogenous Creatinine Clearance and Free Water Reabsorption* ($T^{C}_{H_2O}$)

Patient	Creatinine ml./min. (range)	$T^{C}_{H_2O}$ ml./min. (mean)	Correlation coefficient	No. of periods	p
4	21- 46	.7	.86	11	$<.01$
5	72- 97	2.6	.70	7	.3
3	79-120	2.21	.57	16	.03
7	51- 90	2.13	.65	12	.04

Creatinine clearance was determined only in those periods following mercurial administration in which urine flow rate exceeded 2 ml./min.

The variations in free water reabsorption that were observed in the subjects of this study were not related to urine flow rate or to the rate of solute excretion, which suggests that varying degrees of mercurial effect do not influence this water transport mechanism. The only measured variable that did relate significantly to free water reabsorption was the endogenous creatinine clearance. The mechanism of this relationship is not clear, and further study is necessary to determine whether this phenomenon is characteristic only of the subject with heart failure.

Grossman et al.[11] showed that normal subjects had a greater free water reabsorption during the descending phase of mercurial effect than they had at the same urine flow rates while mercurial effect was reaching its peak. This relationship was not present in the patients in this study. It is conceivable that the variations in free water reabsorption noted in Grossman's data reflected cyclic variations in renal hemodynamics due to mercurials, and were thus of the same mechanism as those in the patients in this study. Further study is necessary to show whether they reflect another phenomenon, not present in the patient with congestive heart failure.

Further comparison between the diureses observed in the patients in this study and those previously described in normal human subjects reveals that the irregular response

manifested in these patients resembles that described by Duggan and Pitts[15] in normal subjects given mercurial diuretic without prior saline loading. In that study, the irregularity of flow following the mercurial administration related to changes in glomerular filtration rate. The correlation between flow rate and endogenous creatinine clearance in the patients of the present study supports the contention that variation in glomerular filtration rate is an important determinant of mercurial effect.[15, 16]

Summary

Mercurial diuresis in patients with congestive heart failure has the characteristics of a simple osmotic diuresis in that there is a linear relationship, with a slope of unity, between osmolal clearance and urine flow rate. The implication of this relationship is that the ratio of water-to-solute loss during such a diuresis depends on the capability for free water reabsorption and the urine flow rate.

Variations in mercurial effect are shown to correlate with endogenous creatinine clearance and are like those observed in normal subjects given mercurials without previous administration of a salt or water load.

Variations in free water reabsorption are shown to relate significantly to endogenous creatinine clearance in 3 of 4 patients. No correlation between free water reabsorption and other parameters such as plasma osmolality, the phase of diuretic effect, or urine flow rate could be demonstrated.

Evidence is presented to confirm the previous finding that the patient with congestive heart failure deprived of water for 12 hours is under maximal antidiuretic effect.

Summario in Interlingua

Diurese mercurial in patientes con congestive disfallimento cardiac ha le characteristicas de un simple diurese osmotic: il existe un relation linear—con un inclination trigonometric del valor 1—inter le clearance osmolar e le intensitate del fluxo de urina. Isto significa que le proportion inter aqua e le perdita de soluto durante un tal diurese depende del capacitate de reabsorption de aqua e del intensitate del fluxo de urina.

Es monstrate que variationes in le effecto mercurial se correlationa con le clearance de creatinina endogene e es simile al variationes observate in subjectos normal qui recipe mercuriales sin administration anterior de un carga de sal o aqua.

Es monstrate que le variationes in le reabsorption de aqua es relationate significativemente al clearance de creatinina in 3 ex 4 patientes. Non esseva possibile demonstrar un correlation inter le reabsorption de aqua e altere magnitudes, como, per exemplo le osmolaritate de plasma, le phase del effecto diuretic, o le intensitate del fluxo de urina.

Es presentate datos que confirma le previe constatation que le patiente con congestive disfallimento cardiac qui es private de aqua durante 12 horas se trova exponite a un effecto antidiuretic maximal.

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Calabresi, P., and Abelmann, W. H.: Porto-Caval and Porto-Pulmonary Anastomoses in Laennec's Cirrhosis and in Heart Failure. J. Clin. Invest. **36**: 1257 (Aug.), 1957.

Injection studies were performed in cadavers to identify portal venous anastomoses to the thorax. Such anastomoses were prominent in cirrhotic cases. These consisted of anastomoses between the short gastric and coronary veins to the esophageal veins of the mucosa and of the venous plexus around the esophagus. The last named plexus was joined to the mediastinal, pleuropericardial and azygos veins by further anastomoses. In 4 cases mediastinal veins anastomosed to bronchial veins. Twice the injected mass reached pulmonary veins and left atrium. Although similar findings were observed in heart failure they were always less marked. No injected substance reached pulmonary veins. Both porto-caval and porto-pulmonary shunts were thus observed. These may act to by-pass lungs with resultant low arterial oxygen saturation.

Oppenheimer

Anatomic Variations of the Auditory Canal Pertaining to the Fit of Stethoscope Earpieces

By Dale Groom, M.D., and Waddy Chapman, M.D.

Leaks in the enclosed acoustical system of the stethoscope reduce its efficiency and can greatly impair the physician's ability to detect the faint murmurs of early valvular heart disease. The results of this study demonstrate a high degree of variability in size and configuration of the external auditory meatus among different individuals. It appears probable that both excessive leaks and also partial or complete occlusion of the acoustical pathways commonly result with the use of standard stethoscope earpieces.

IN A RECENT study on auscultation[1] differences of considerable magnitude were noted in the auscultatory thresholds of 40 physicians listening to a heart murmur. The intensity levels required for audibility of the murmur were 10 to 20 times higher for some subjects than for others. It was evident in this experiment that not all such differences in auscultatory proficiency were attributable to individual differences among the physicians in hearing acuity, professional training and experience, and psychologic reactions. Efficiency of the various stethoscopes employed—and particularly sound leaks around the earpieces—appeared to play a major role in some cases.

The undesirable effects of "leaks" in the enclosed acoustic system of the ordinary stethoscope have been discussed by Rappaport and Sprague,[2] both as to the consequent decrease in efficiency of sound transmission and the increased interference by room noise. One source of leaks, certainly, is ill-fitting earpieces. The purpose of the study to be described was to measure the degree of anatomic variation in the size and configuration of normal external auditory meatuses, and to determine to what extent one can expect a stethoscope earpiece of standard size to function efficiently in a variety of ear canals.

Method

Ten male medical students served as subjects for this experiment. By means of a plastic impression material of the type used commercially in the fashioning of hearing-aid earpieces, 2 sets of casts were obtained from both ear canals of each subject: 1. A rigid "head halter" apparatus (fig. 1) was constructed which could be oriented on each subject in a uniform position, with use of bony landmarks of the skull as points of reference. Blunt pins projecting from this apparatus were incorporated into the first set of impressions while they were still soft, in order that the casts could be re-oriented subsequently for measurement of the directions taken by the axes of the meatuses. 2. Each subject was asked to put on the same stethoscope in his customary position of use. A second set of impressions was then made with this in place, incorporating the stethoscope earpiece directly into the casts.

Measurements of the direction and dimensions of the canals where the stethoscope earpieces rested were made on the first set of impressions and are set forth in table 1.

The second set was carefully inspected and analyzed to determine where leaks might occur around the earpieces and where there might exist total or partial occlusion of the earpiece apertures by misalignment in the canals.

Results and Discussion

In each case the stethoscope earpiece was found to rest not in the meatus proper but in the apex of the funnel formed by the concha, with its aperture adjacent to the orifice of the cartilaginous meatus (fig. 2).

The anatomy of the external ear has been described in detail by Bezold and Siebenmann.[3] Axis of the concha, the funnel-shaped cartilaginous portion of the external ear bounded anteriorly by the tragus, is directed anteriorly and superiorly, its apex opening into the lateral cartilaginous portion of the meatus proper which is directed posteriorly, forming an angle with the concha. (A second bend, in the opposite direction, takes place between the cartilaginous lateral meatus and the medial osseus portion, but is not involved

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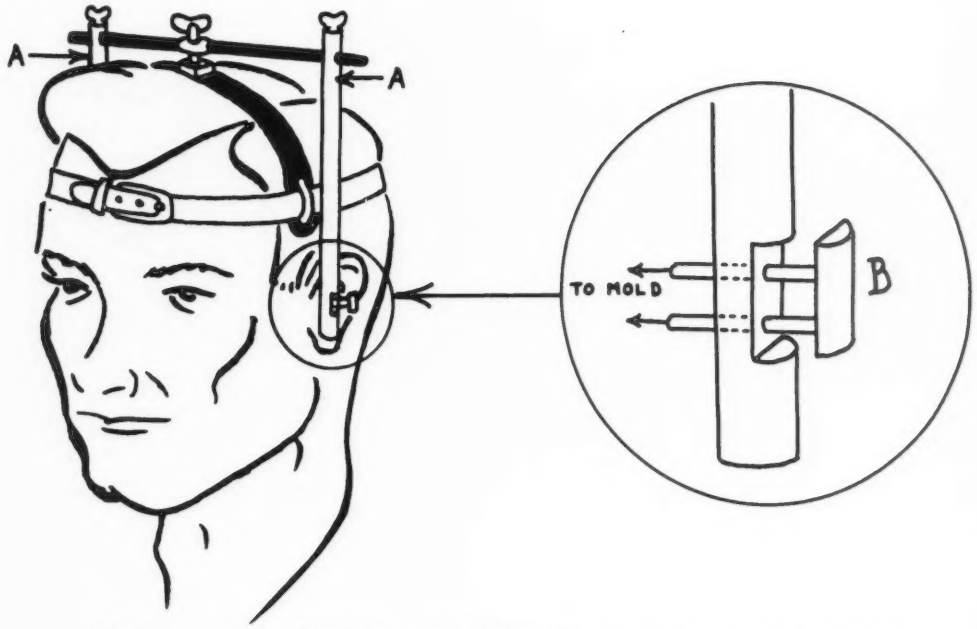

FIG. 1. Apparatus for determining contour of the auditory canal, showing pins incorporated into plastic mold for orientation.

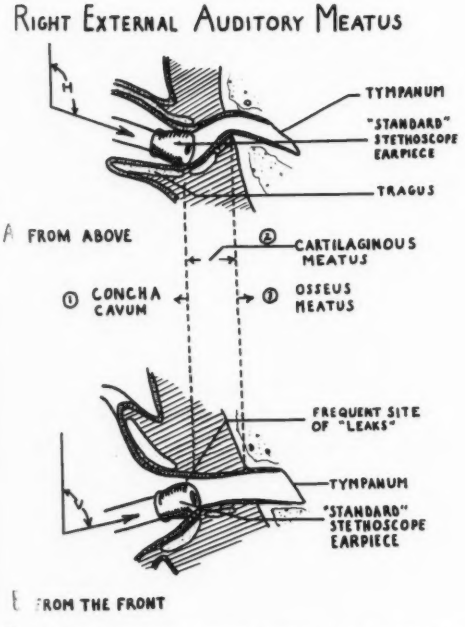

FIG. 2. Location of stethoscope earpiece in external ear.

in the fit of stethoscope earpieces.) This first bend is of interest because an earpiece that is too small may rest so deeply in the concha that its aperture is occluded by the anterior wall of the cartilaginous meatus. In 6 of our subjects it appeared from the second set of impressions that partial occlusion of this type was probable, 4 of them showing considerable occlusion bilaterally. Total occlusion in 1 ear or the other appeared to be imminent in 2 of the subjects.

Cross sections of molds of the concha at the point where the earpieces rested revealed its shape to be elliptical in all subjects. The average size was 11.8 by 8.0 mm. with the long dimension directed vertically. However, marked variation in size was observed, the largest being 14.2 by 10.1 mm., the smallest 8.2 by 6.2 mm. Comparison of measurements of the 2 ears in individual subjects showed discrepancies of up to 2.4 mm. in the long dimension, and 1.3 mm. in the smaller one. This irregularity of shape and variation in size might well be responsible for leaks, and indeed the second set of impressions showed that in 14 of the 20 ears measured the apposi-

TABLE 1.—*Measurements of External Auditory Canals in Ten Subjects*

Subject	Angle "V" (degrees)		Angle "H" (degrees)		Dimensions of concha cross section		Occlusion of aperture		Leaks	
	R	L	R	L	R (mm.)	L (mm.)	R	L	R	L
1	70	63	123	119	11.8× 8.8	9.4× 7.9	prob.*	0	+	
2	62	56	124	117	12.2× 9.5	10.9× 8.2	prob.	prob.		+
3	49	43	103	103	12.8× 7.5	13.3× 8.2	0	total	+	+
4	52	57	109	114	8.4× 6.2	8.2× 6.2	0	0	+	
5	86	79	102	97	11.9× 6.8	12.3× 7.5	0	0		+
6	74	64	112	109	14.2×10.1	14.0×10.0	prob.	prob.	+	+
7	78	82	115	122	12.5× 8.5	11.8× 7.2	prob.	prob.	+	
8	70	68	118	124	10.4× 7.2	10.9× 8.5	0	0		+
9	47	51	127	130	12.6× 7.8	13.7× 9.1	prob.	total	+	+
10	73	68	102	106	12.1× 7.9	12.8× 7.1	prob.	prob.	+	+

*Probable.

tion of earpiece to canal wall was judged to be poor in at least 1 point.

It is evident in table 1 that the axis of the concha, though generally directed somewhat anteriorly and superiorly, showed considerable variation among the 10 subjects. This variation was as much as 43° in the vertical plane (angle "V" in fig. 2) and 33° in the horizontal plane (angle "H"). Direction of the canals in a given subject, however, was more uniform with no variation of greater than 10° in the vertical or 7° in the horizontal plane. Thus the angle of direction of earpieces, as well as their size and shape, would appear to be instrumental in determining stethoscope efficiency.

SUMMARY

Plastic casts of the external auditory meatuses of 10 subjects were studied. Impressions were made both with and without "standard" stethoscope earpieces in place. Considerable variation was demonstrated among the subjects in size and conformation of the meatus.

Remarkably poor fits of earpieces, probably resulting in excessive leaks and partial or complete occlusion of earpiece apertures, were observed in more than half the impressions. The amount of "give" of the ear structures is uncertain, but it would appear that effective stethoscope efficiency might be appreciably improved by more allowance for individual anatomic variations of the auditory canal in the design of stethoscope earpieces.

SUMMARIO IN INTERLINGUA

Esseva modulate copias plastic del externe meatos acustic de 10 differente subjectos. Le copias esseva facite con a sin auriculares "standard" de stethoscopio in position. Considerabile variationes esseva demonstrate inter le varie subjectos con respecto al dimensiones e al conformation del meatos.

Esseva observate in plus que un medietate del casos un multo imperfecte adjustation del auriculares, resultante—probabilemente—in un considerabile escappamento de sono e in le complete o partial occlusion del aperturas del auriculares. Le grado del adaptabilitate del structuras del aure es incerte, sed il pare que le efficacia del uso de stethoscopios pote esser augmentate considerabilemente si le construction de auriculares stethoscopic es guidate plus extensemente per le consideration de variationes anatomic individual del canal auditori.

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CLINICAL PROGRESS

Clinical Use of the Percutaneous Renal Biopsy

By JOHN D. ARNOLD, M.D., AND BENJAMIN SPARGO, M.D.

SINCE THE FIRST practical method of renal biopsy by the percutaneous route was developed,[1, 2] at least 2,000 cases have been recorded. Perhaps several times that number of biopsies have actually been performed. Although the percutaneous renal biopsy is well established as a research procedure, it is not so well established as an ordinary diagnostic procedure. It is the purpose of this review to discuss the use of the percutaneous renal biopsy as a diagnostic tool and to discuss the changes in concept of renal disease that have resulted from its use in investigation.

RISKS AND INDICATIONS

As with all operative procedures, the percutaneous renal biopsy carries certain risks. Even though local conditions vary widely a limited evaluation of the risk is feasible. In at least 3 institutions a series of 500 or more biopsies without mortality has been accumulated. In many other institutions the percutaneous renal biopsy has been performed in 200 or more cases without mortality. On the other hand several deaths have occurred on the first attempt or in a small series. The natural reluctance to report this tragedy has kept some of this experience from the literature. It would appear that in experienced hands the risk of mortality should be less than 0.1 per cent.

In several of those deaths that have been reported or are known to us the actual mechanism of death is not known. Several reported deaths may have been unrelated to the biopsy procedure. Of the known causes of death, hemorrhage and shock are of first importance.

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Morbidity, however, has been experienced in almost every series. Hemorrhage of some degree probably occurs after every biopsy. In terminal or near terminal patients an antemortem biopsy is accompanied by evidence of blood loss ranging from 10 to 50 ml. The local tissue forces in the region of the posterior aspect of the kidney seem quite capable of tamponade and control of this amount of bleeding.[3] In most cases the only evidence of bleeding from the biopsy site is the appearance of blood in the urine. Hematuria is usually microscopic in amount and persists no longer than 36 hours. Bleeding produced by transection of small arteries in the kidney has occasionally been observed. These hemorrhages usually halt spontaneously.

More serious accidents also occur. Occasionally the needle has been known to pentrate the pelvis of the kidney. This is discovered by the reflux of urine through the biopsy needle or from recovery of mucosal tissue in the biopsy specimen. Although this would seem to be a serious event it is usually uncomplicated unless the urinary tract is obstructed. Occasionally the hilar vessels have been opened by the percutaneous needle. Bleeding from this source is potentially serious, especially if the renal vein is involved. Although bleeding from the hilar vessels is more serious than from others, hemorrhage from any source may be alarming. Hemorrhage has on occasion required operative intervention for control. The incidence of severe hemorrhage requiring some form of treatment (transfusion or surgery) has been surprisingly low. Significant bleeding occurs less frequently than once in 100 biopsy attempts. Many of these severe hemorrhages are self limited and require only simple trans-

fusion. It has been thought that the incidence of hemorrhage is much higher in cases of malignant hypertension, uremia, primary bleeding dyserasias, obstructive uropathies, and polycystic disease.

Immediate or delayed pain occurs in a small number of patients. The pain may be either colicky or it may be constant and localized in the flank. It is rarely severe.

Edema does not by itself seem to increase the risk of the percutaneous biopsy; many patients with the nephrotic syndrome have been biopsied without difficulty. It is also surprising that infections in and around the kidney are apparently not complicated by biopsy. Fever after biopsy even in the presence of pyelonephritis is extremely rare.

The size or age of the patient also does not seem to limit the procedure. At least 1 patient of 450 pounds, has been biopsied successfully.[3] The percutaneous renal biopsy has been carried out successfully at every age from 1 year into the seventh decade. It is probable that at both ends of this age range the risks are increased. It is usual though not always necessary in smaller children to carry out the procedure under heavy sedation or anesthesia.

In addition to certain reservations in the selection of patients with hypertension, bleeding dyscrasias, etc., a careful study of the x-ray films of the kidney will probably prevent a small number of accidents that would occur because the kidney is in an abnormal location. A single kidney would seem to be sufficient cause for avoiding a biopsy. It also appears to be a sound practice to carry out the procedure in the hospital and to keep the patient under observation and at bed rest for 48 hours subsequent to the biopsy.

Several methods of doing the biopsy have been described. At the present time the Franklin modification of the Vim Silverman needle is probably most widely used. The patient is usually placed prone with his abdomen on a sand bag. This position seems to immobilize the kidney partially. With an exploratory spinal needle the kidney may be located by the respiratory excursions of the needle, once the needle reaches the kidney. In most patients the capsule of the kidney is perceived by the type of resistance it offers the needle. Specific technics are discussed elsewhere.[4]

With all known precautions and with experience a small mortality (of the order of 1 in 1,000 cases) appears to be the minimum risk. This being so, when is the percutaneous renal biopsy indicated as a diagnostic procedure?

The Problem of Making a Clinical Diagnosis

Unless a patient is in uremia or in the nephrotic syndrome, the primary renal diseases are remarkably asymptomatic. Obviously a patient with lupus nephritis may have other stigmata of systemic lupus erythematosus; a patient with the Kimmelstiel-Wilson lesion will probably have overt diabetes; but a large number, perhaps the majority of patients with primary renal disease who are accustomed to receive close medical attention are discovered by routine urinalysis. This appears to be less true of children than of adults.

In a patient without signs or symptoms there are relatively few abnormalities of the urine which help in formulating a specific diagnosis. The list of such findings is unfortunately quite short.

Red cell casts and hemoglobin casts have long been interpreted as indicating an acute glomerulitis. Albuminuria greater than 5 Gm. per 24 hours usually indicates one of the diseases capable of producing the nephrotic syndrome. This is also true of birefringent fat in cells and casts. Glitter cells are often associated with pyelonephritis. Papillae in the urine are a good though very rare sign of acute necrotizing papillitis. Bacteria in a fresh clean urine suggest chronic pyelonephritis. Hemosiderin in cells suggests a form of renal siderosis.

Other laboratory findings in an asymptomatic patient are also of assistance. A high blood globulin points strongly to amyloid or systemic lupus; a low albumin suggests an early nephrotic syndrome and usually thou h

not invariably limits the diagnosis to those diseases which produce this syndrome. The finding of L. E. cells suggests lupus. Long-standing chronic infection suggests amyloid. Most laboratory findings only suggest a renal disease; usually they do not establish a specific diagnosis.

Even patients with marked renal insufficiency and uremia and patients with the nephrotic syndrome may have little to suggest a specific diagnosis. Any one of a large number of disease entities may produce the nephrotic syndrome. A list of diseases producing the nephrotic syndrome should include lipid nephrosis, chronic glomerulonephritis, systemic lupus, diabetes mellitus, polyarteritis nodosa, renal vein thrombosis, amyloid disease, and certain drugs and toxins. The nephrotic syndrome has been reported to occur with other entities but this occurs rarely and the possibility always exists that a primary renal disease of another sort was overlooked. The pure lipid nephrosis, for instance, may be diagnosable only by the electron microscope.

Although every biopsy attempt involves risk, it does not always produce a diagnostic piece of tissue. From 60 to 90 per cent of all biopsy attempts produce from 5 to 30 or more glomeruli. This varies from operator to operator. Although this may be sufficient tissue to give a very useful and spectacular diagnosis, it may also contribute nothing of clinical value.

The small size of the biopsy specimen often forces a great deal of attention on 1 or 2 elements of the total pathologic process. This results in a change in emphasis over that of the study of pathologic anatomy on large sections of kidney. In some respects the renal biopsy gives a worm's-eye view of renal pathology. The discussion that follows emphasizes single-element pathology and is organized as follows: (1) membranous glomerular lesion, (2) proliferative glomerular lesions, (3) vascular changes, (4) intracytoplasmic changes, (5) tubular changes, and (6) interstitial changes. Pathologic lesions in these areas give the most help in making a diagnosis. It is obvious of course that a change of any one type is related to changes in all areas of the nephron. Membranous glomerular changes lead to proteinuria; the increased urinary protein is frequently accompanied by hyaline droplet changes in the tubules. Tubular retrogressive changes may lead to atrophy with condensation of the stroma in which case vascular involvement could be produced. In a similar fashion glomerular proliferative or vascular changes could start the cycle.

The Problem of Pathologic Interpretation

Several factors contribute to the problem of interpreting the pathologic changes found on renal biopsy and diminish the usefulness of the biopsy procedure. In part this is due to the lack of a depth of general experience in interpreting renal biopsy material and the current lack of agreement between the classical pathologic and clinical entities. Almost every group with extensive experience with the renal biopsy has had early difficulty in specifically characterizing changes that are obviously pathologic and relating them to current pathologic concepts. Some of this difficulty resolves as local experience accumulates, but some is apparently due to the lack of recognized standards for many stages of disease which heretofore were seen at the autopsy table only, and then usually in the terminal period of the disease. These difficulties are being resolved by serial renal biopsies in long-term studies with good clinicopathologic correlation.

Some of the problems of interpretation are currently insurmountable and no clear way of overcoming them is now apparent. The biopsy sample is usually taken at random. If the lesions are focal and scattered they will be discovered only by chance. The lesions of Kimmelstiel-Wilson disease and scleroderma, for example, are often so focal that a very large specimen would be needed to insure inclusion of a diagnostic lesion. Others, such as glomerulonephritis, with more uniform diffuse involvement will be discovered if a reasonably good sample is obtained. Although the electron microscope is not generally con-

sidered a clinical tool, its role in the resolution of some of the problems of the renal pathology has become very important, for it provides information that is not currently available in any other way. The problem of random sampling is magnified several fold in studies with the electron microscope. Because if its increasing importance the findings with electron microscopy will be discussed along with those of light microscopy.

Membranous Lesions of the Glomerulus

One of the most intriguing problems in renal physiology and consequently in renal pathology has to do with the role of the basement membrane in the separation of the colloid elements of the blood from the crystalloids and water. This filtration presumably occurs across the basement membrane. A disturbance in filtration leads to the most important clinical signs of renal disease, namely, azotemia and proteinuria. The light microscope even with the best of stains does not reveal enough of the structure of the basement membrane to indicate the physiologic function that is disturbed in any given disease entity. In fact, in at least one important disease with heavy proteinuria (lipid nephrosis) the basement membrane may on occasion appear to be normal by light microscope.

In a number of other diseases the basement membrane appears to be thickened. Some types of basement membrane thickening have a characteristic appearance. Of these systemic lupus erythematosus and the early changes in the diabetic kidney are probably the most important. In contrast to these conditions a number of patients have alterations of the basement membrane which must be classified simply as membranous glomerulonephritis. The clinician sometimes has a difficult time relating this pathologic diagnosis to the established clinical entities. At the present time it is clear that for a number of patients with membranous glomerulonephritis a clear pathologicoclinical correlation has not been made. It is possible that some of these represent a new and as yet undescribed entity. It would of course be unsound to fasten on the changes of the basement membrane as the pathognomonic feature of most renal diseases but in the absence of other changes such as cellular proliferation, etc., the basement membrane may be the only feature upon which to build a diagnosis. Frequently membranous glomerulonephritis becomes a miscellaneous category of renal diseases known to be associated with the nephrotic syndrome.

Lipid Nephrosis

For nearly 30 years the diagnosis of lipid nephrosis has been the subject of controversy. Until specific changes were revealed by the electron microscope there were no pathologic or clinical features with enough specificity to convince all observers of the existence of this entity. Frequently, in the early stages of the disease, no pathologic abnormalities could be determined in the glomerulus with use of the light microscope. Some observers have even thought this to be a variant of chronic glomerulonephritis.

The electron microscope has changed all this. To understand the changes that are now attributed to lipid nephrosis,[5] one has also to understand the anatomy of the basement membrane and the associated endothelial and epithelial cells which compose the filtering apparatus of the glomerulus (fig. 1). Normally the basement membrane is approximately 0.1 μ in thickness. It increases in thickness with age and it is apparently derived from the glomerular endothelial cells. The epithelial cells which line the outer surface of the capillary tuft are quite unique at the magnification of the electron microscope. These cells possess many branches which divide into secondary branches or foot processes called podocytes. The podocytes look as if they provide mechanical support for the basement membrane.

In lipid nephrosis the foot processes are smudged and confluent, with little other change in the glomerular capillary. Unfortunately this can be determined only at a magnification produced by the electron microscope. This means that in the ordinary survey of patients in the nephrotic syndrome or

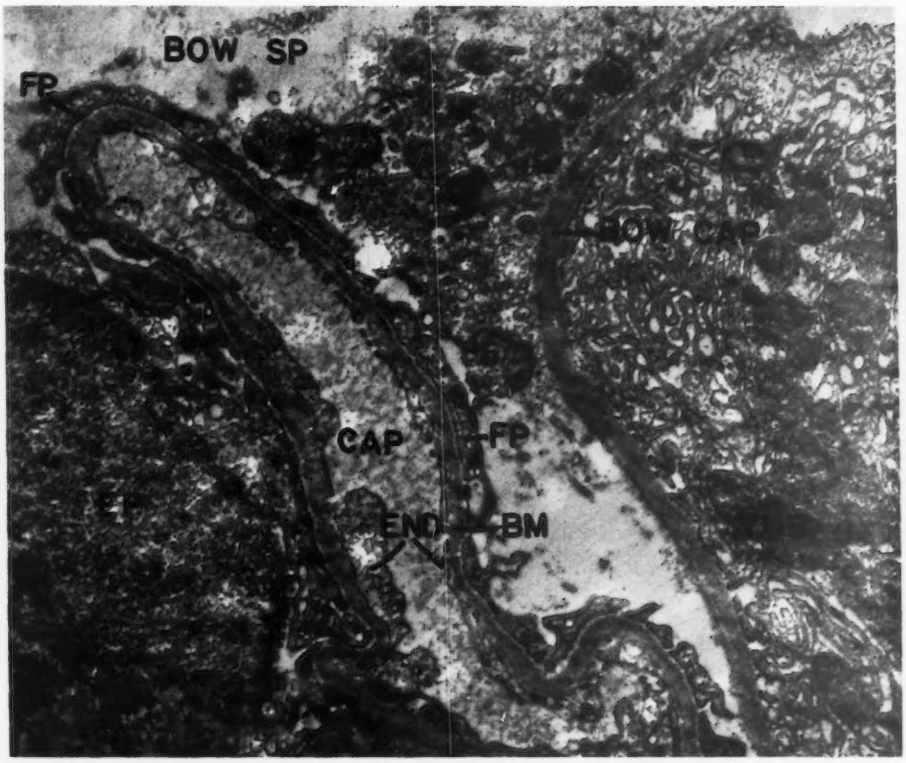

FIG. 1. A portion of a glomerulus from a 5-year-old child with lipid nephrosis in clinical remission. The foot processes (FP) of the epithelial cells (EP) are fused with a dark, nearly solid layer of cytoplasm covering the basement membrane (BM). The basement membrane is slightly thickened. The endothelial cytoplasm (END) has conspicuous pores. (Osmium fixation) × 11,500.

of patients who have a clinical spectrum that can be associated with lipid nephrosis a specific pathologic diagnosis may not be made by the light microscope except by exclusion. The specific lesion demonstrated by the electron microscope now must be correlated with the actual clinical course of these patients. It would be premature at this time to translate previous clinical experience with the disease entity of lipid nephrosis to the present group of patients with lipid nephrosis diagnosed by the electron microscope.

One group of authors has reported the disappearance of albuminuria by therapy with steroids to be associated with a return to normal of the podocytes in the glomerulus.[6] We have observed, however, 2 patients in distinct remission of the disease in whom the confluent, smudged podocytes were still marked. The disturbance of podocytes would not seem to be sufficient to account for the massive albuminuria frequently seen in this disease.

Systemic Lupus Erythematosus

Although this disease has many striking and bizarre clinical features and sometimes is an easy clinical diagnosis, there is an increasing number of patients now recognized in whom the onset of the disease is either so insidious or the symptom complex so unusual that a diagnosis cannot be made immediately. The natural history of systemic lupus is undoubtedly much longer than it was once thought to be,[7] and it is quite possible that the disease may present as a nephritis of ob-

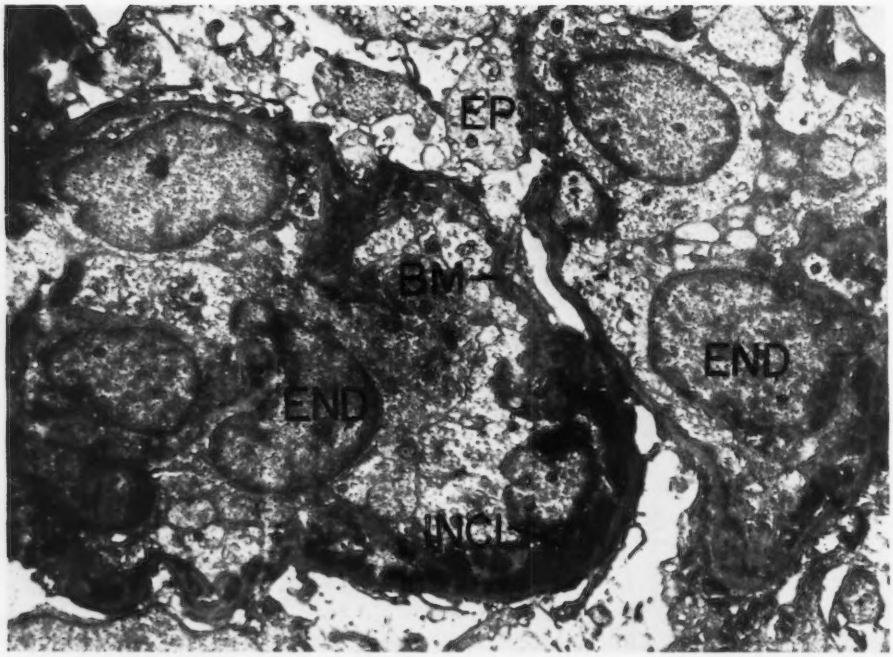

FIG. 2. Changes in the glomerular capillary of a 45-year-old woman with a 1-year history of systemic lupus erythematosus. There are proliferative endothelial cell changes (END), osmophilic inclusions (INCL) in cytoplasm of endothelial cells at the basement membrane (BM), occlusion of the capillary lumen, and mild thickening of the basement membrane. This glomerulus was severely damaged and other areas had fibroepithelial crescents. × 9,500.

secure etiology, or in fact it may present with obscure symptoms with few findings in the urine. In either case, with or without an abnormal urine, a diagnostic anatomic change may exist in the kidney. Lupus nephritis, unlike many of the other nephropathies, does not produce a urinary sediment that is easily correlated with the degree of activity in the kidney tissue itself. When wire-loops are clearly identified, there is generally little difficulty in making a diagnosis. Unfortunately, glomerular changes such as proliferation of the endothelial and epithelial cells, generalized thickening of the basement membrane, hyaline thrombi, focal necrosis, fibroepithelial crescents, fibrinoid changes, and so on, all of which are not clearly pathognomonic of systemic lupus, may be all that is discovered on renal biopsy; the diagnosis may remain in doubt despite a fairly large biopsy. If, as occasionally happens (10 per cent), a hemotoxophyl body is found, the diagnosis is secure.[8] Figure 2 shows changes in the glomerular capillary of a patient with lupus as seen under the electron microscope.

Chronic Glomerulonephritis

Chronic glomerulonephritis has been a popular clinical diagnosis for many years in patients who present few systemic complaints but in whom there is evidence of nephritis not due to primary infection or hypertension. It may be, as suggested by Earle and Seegal,[9] that chronic glomerulonephritis is due to a number of different causes; if so, we must then consider the diagnosis of chronic glomerulonephritis as a pathologic diagnosis with the kidney reacting in a single manner to different stimuli. It is our impression that chronic glomerulonephritis is much less common than one would predict on the basis of autopsy studies. This is probably due to the fact that much earlier lesions are being seen by percutaneous biopsy than are seen at

he autopsy table. The stigmata of other disease may now be more easily and frequently dentified. This has cut heavily into the group previously diagnosed as chronic glomerulonephritis. On the basis of the membranous hanges a specific diagnosis of chronic glomerulonephritis cannot be made (fig. 3). It is necessary to show, in addition to the membrane changes, endothelial or epithelial cellular proliferations. It is helpful to have synechia and hyalinization of the glomeruli. t is unfortunate that no pathognomonic feature, either clinical or histologic, exists for chronic glomerulonephritis so that some landmark may be used to establish the proper boundaries of this entity. At the present time it is not even possible to depend on the history of the patient, for it is rare to find one who gives a definite history of an acute episode of glomerulonephritis. In fact it is not even certain how often an episode of acute glomerulonephritis actually initiates the chronic disease.

Diabetes Mellitus

The concept of diabetic renal disease is also undergoing a considerable evolution. For a long time the initial and prominent feature of diabetes was the disturbance of the carbohydrate metabolism of the patient. It is becoming increasingly more apparent that specific pathologic changes occur in diabetes which are not associated with overt hyperglycemia or even at times with an abnormal glucose tolerance test. This has been clearly recognized for several decades in the case of necrobiosis lipoidica diabeticorum.[10] This skin lesion may antedate the discovery of an abnormality in carbohydrate metabolism by a number of years. It is also well known that encephalopathy antedates the discovery of the typical findings of diabetes.

In the past it has been common to attribute the renal disease of diabetes to the longstanding disturbance in carbohydrate metabolism. It has been suggested that nephropathy is made worse by poor control. However, with the advent of the renal biopsy and access to kidney tissue in patients who may be observed over a long period of time, it is now apparent that renal lesions characteristic of diabetes mellitus may occur prior to the onset of the disturbance in carbohydrate metabolism.[11]

Unfortunately the changes in the diabetic kidney are very complicated. It is probable that the several types of pathologic change seen in diabetes are not even very closely related. It appears that the vascular changes, the glomerular changes, tubular changes, and interstitial changes may occur in several different sequences. The severity of any one change does not correlate well with the severity of another. One change in the glomerular basement membrane as seen on biopsy is well correlated with the overt state of diabetes mellitus, and offers the best starting place from which to unravel the complexities of the diabetic kidney.

The change known as the Kimmelstiel-Wilson lesion,[12] which is a nodular cellular lesion, is one of the very few pathognomonic lesions of the kidney. Actually the description of the Kimmelstiel-Wilson lesion in the past has been dependent upon the light microscope and a fairly advanced lesion has been necessary for clear identification. As it has been more recently studied by the electron microscope the Kimmelstiel-Wilson lesion appears to begin as an intracytoplasmic change in the endothelial cell.[13] These changes would appear to be diagnostic. The important thing, of course, is that the cytoplasmic changes may be seen to involve the basement membrane and eventually to produce the intralobular nodule of the classical Kimmelstiel-Wilson type. The recognition of less extensive lesions by electron microscopy has made it possible to reinterpret the light microscope findings and to identify much earlier lesions with the light microscope.

The interpretation of the frequently prominent vascular changes in diabetes is very difficult. Hyalinization of the efferent arteriole is a characteristic[14] that is often useful in larger sections but is much less useful with the biopsy specimen. There is otherwise nothing in the nature of the vascular changes that distinguishes them from the changes also due to aging or hypertension. The vascular

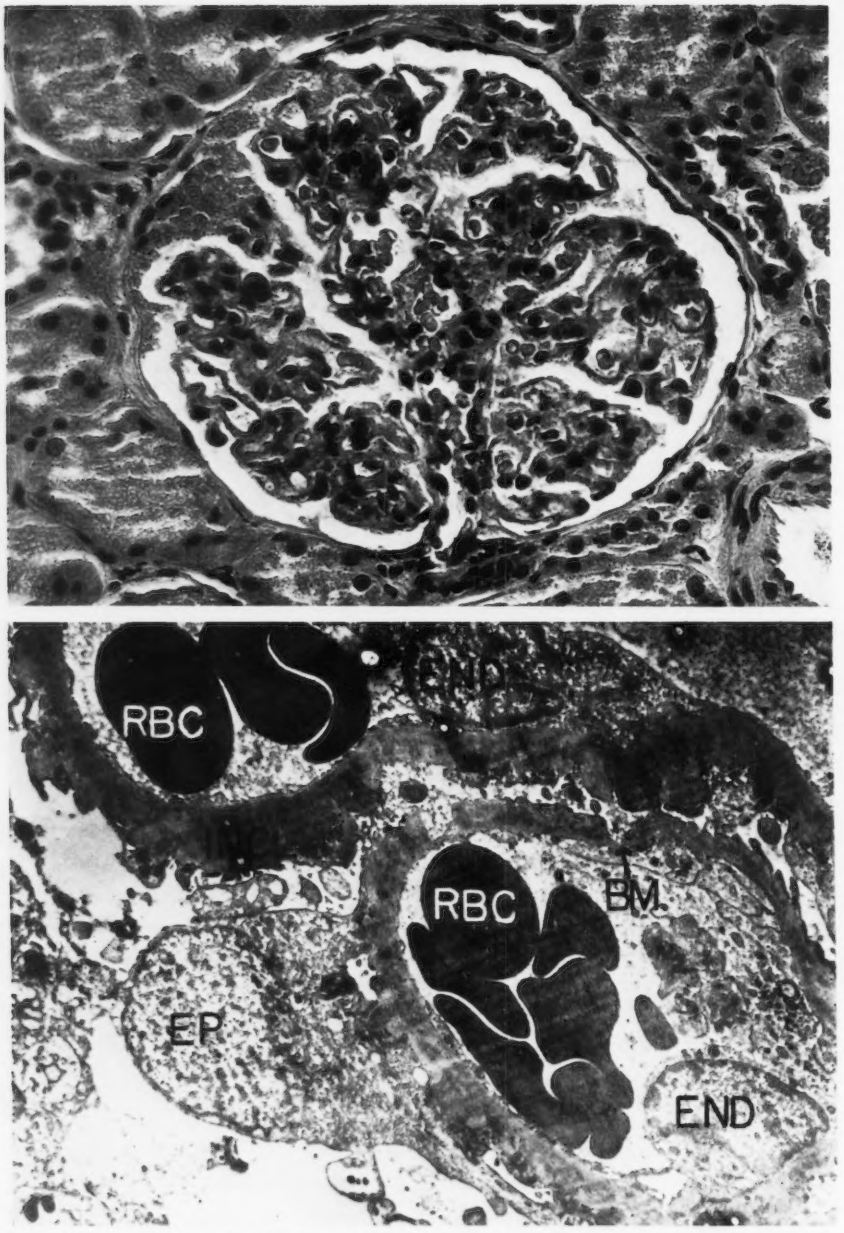

FIG. 3. *Top.* A glomerulus showing extensive nonspecific membranous glomerulonephritis from a 28-year-old man with a 2-year history of fatigue and nephrotic syndrome. These lesions are difficult to distinguish from lupus nephritis by light microscopy. The electron micrograph however is quite different from systemic lupus erythematosus, as is shown in figure 3*B*. (Hematoxylin and eosin) × 430. *Bottom.* Two glomerular capillaries showing the extensive accumulation (INCL) of material along the basement membrane (BM) extending into the cytoplasm of the epithelial cells (EP). The electron micrograph distinguishes this lesion from the lesion shown in figure 2, which we believe to be typical of systemic lupus erythematosus. It has not yet been possible to correlate this anatomic change with an accepted clinical entity. × 10,000.

esions, therefore, are not specific in type nd their presence does not usually make a pecific diagnosis.

Since some of the relationships between athologic changes in the kidney are yet uncertain, they must be interpreted with this ncertainty in mind. The diffuse membranous lesion of Bell,[14] which he believes to ntedate the nodular Kimmelstiel-Wilson esion, the hyalin acellular fibrinoid lesion of oss, sometimes called the glomerular fibrinoid cap, or the exudative lesion of the glomeruli in diabetes and some of the tubular lesions, particularly those described by Kimmelstiel recently, have yet to be accorded a high degree of specificity. Micro-aneurysms in the glomeruli are frequently associated with the specific nodular Kimmelstiel-Wilson lesions and retinal aneurysms.

To complicate the problem further, patients have now been observed with diabetes in whom renal damage is apparent without an abnormal urinary sediment.[3] This dissociation of the histology and clinical findings can be discovered only by renal biopsy.

Amyloid

Occasionally the discovery of amyloid will come as a surprise; more often, however, it can be suspected because of the presence of a chronic infection or debilitating disease. Occasionally this histologic diagnosis will require special stains of the kidney tissue. Also, early lesions of amyloid may be confusing. In our material an extension from either side of the basement membrane of the glomerular capillary has been demonstrated by electron micrographs of an early lesion before the light microscope reveals amyloid deposits. The electron micrograph once more plays a real though limited role in making a diagnosis. The kidney biopsy now ranks in importance with the liver biopsy as a means of making a diagnosis of visceral amyloid.

Toxemias of Pregnancy

These entities have presented long-standing difficulties in diagnosis in the past. It is obvious that pre-existing renal disease may contribute to the clinical picture seen in pregnancy, and it is also obvious that some of the renal changes are produced by the pregnancy itself. A large series of renal biopsies examined by the light microscope have consistently failed to separate other renal diseases from eclampsia.[15] It will remain to be seen what the electron microscope can do to separate these conditions from eclampsia, but it is clear that occasionally the signs of chronic glomerulonephritis or pyelonephritis will be discovered and the diagnosis therefore made.

PROLIFERATIVE GLOMERULAR LESIONS

Acute Glomerulonephritis

One concept of acute glomerulonephritis is that of an inflammation of glomerular capillaries accompanied by a striking acute proliferative change of the cells and a varied amount of exudation. Endothelial change is frequently most marked but epithelial proliferation is common.

It is thought that the clinical diagnosis of acute glomerulonephritis is a fairly clear diagnosis. A history of upper respiratory infection, hematuria, recovery of the β-hemolytic streptococcus, an elevation of the antistreptolysin-titer, and the characteristic facial edema, hypertension, and reduced kidney functions give a high order of confidence about the diagnosis. Unfortunately, this constellation of clinical and laboratory findings is not always complete or unequivocal. It is probable that an exacerbation of chronic glomerulonephritis, obstructive uropathies, focal nephritis, and acute renal failure have all been confused with acute glomerulonephritis. The appearance of birefringent fat in cells and casts suggests another diagnosis.

Although the acute proliferative and exudative reaction of the glomerulus is most characteristic, tubular and interstitial involvement is frequent. The proliferative change in the endothelium of the glomerular capillaries is a prominent feature producing narrowing of the lumen and ischemia with almost certainly a marked effect on renal blood flow.

From the point of view of the diagnosis of acute glomerulonephritis, the percutaneous renal biopsy is of very great assistance. Since

the disease is uniform and diffuse, a small number of glomeruli may be sufficient to establish the diagnosis. Nonstreptococcal infections have been reported to give a classical pathologic picture of acute glomerulonephritis.[16] Enough uncertainty surrounds many of the cases of presumed acute glomerulonephritis to warrant a percutaneous biopsy. The possibility of a recurrence of chronic renal disease masquerading as an acute episode of glomerulonephritis is often very real.

In addition to making the diagnosis, the biopsies done to date have revealed that glomerular disease persists much longer than was anticipated from the study of the urinary sediment. A case has been observed with resolving glomerular disease as long as 14 months after the urine became free of albumin and formed elements.[3] As a corollary to this, it is quite likely that a number of cases of acute glomerulonephritis with systemic complaints exist in which the urine is normal. We as well as others have seen acute glomerulonephritis presenting both with unexplained episodes of acute hypertension without albuminuria and as an episode of acute anuria. In the latter instance, of course, no useful urinary sediment was obtained.

Chronic Glomerulonephritis

It would be difficult to point to the involvement of any one segment of the renal architecture as being most characteristic of chronic glomerulonephritis. It is true that glomerular proliferation is a prominent component, but widespread scarring is frequently present before the development of clinically recognized symptoms or signs. This disease is diffuse and widespread in the kidneys and renal biopsy is successful in revealing it unless the degree of change is such that specific characteristics are obliterated or become indistinguishable from those of other end-stage kidneys.

Vascular Changes

Differentiation between primary renal disease and renal vascular changes secondary to hypertension is often difficult to establish. A satisfactory separation may be possible by renal biopsy only in cases where proliferative glomerulonephritis clearly antedates the arteriolar nephrosclerosis. The focal nature of the vascular involvement makes biopsy evaluation difficult except in severe hypertensive states. In addition to the difficulty inherent in the interpretation of the pathologic changes the patient with hypertension is a somewhat greater risk for biopsy than a patient with normal blood pressure. However, the percutaneous renal biopsy may provide life-saving information by revealing an unexpected pyelonephritis in a patient with severe hypertension.[17]

Progressive Systemic Sclerosis

Progressive systemic sclerosis, classically considered to be a dermatologic lesion, has been shown to involve the gastrointestinal tract and to involve the kidney. The renal involvement is most pronounced in the intralobular arteries where there is marked acellular intimal thickening with secondary changes in the media. Fibrinoid necrosis may occur and extend to the glomeruli. If the involvement is extensive an infarction may occur.[18] Since the lesions are focal, an evaluation by needle biopsy may be difficult. The differentiation from systemic lupus erythematosus may be made by biopsy as arteriolar involvement is infrequent in lupus as compared to progressive systemic sclerosis. There are occasional changes that are indistinguishable from those of malignant hypertension. Since the major renal involvement is late in the course of the disease, it is unlikely that progressive systemic sclerosis will be diagnosed by renal biopsy before clear stigmata of the disease are apparent in other organ systems. Several cases have appeared, however, with a fulminating course and with predominant involvement of the kidney.

Venous Lesions

In cases with renal vein thrombosis, biopsy may be helpful in support of the diagnosis in spite of the rather nonspecific changes, including interstitial edema, tubular atrophy,

and a diffuse thickening of the glomerular basement membrane.[19] A specific diagnosis of visceral thromboangiitis obliterans may be made occasionally where there is ideal sampling.

Tubular Disease

Except for the Fanconi syndrome and a few other rare metabolic familial disorders, the most important tubular diseases are acute and generally not progressive. If the patient survives the acute episode, an equilibrium compatible with an extended life span is usually achieved. As a consequence, tubular disease (except for these rare hereditary disorders and the complications secondary to chronic pyelonephritis) are of clinical interest chiefly in the management of acute renal failure. Many centers now take biopsies from patients in acute renal failure as soon after the anuria develops as possible.

The anticoagulant therapy during external dialysis increases the risk of hemorrhage from a biopsy made within the previous 24 hours. It appears to be reasonably safe to carry out dialysis 48 hours or so after a biopsy. The usefulness of the information produced by the renal biopsy will of course vary.

After due consideration of the sampling error some prediction about the recovery of the renal lesion is sometimes possible from the biopsy. A number of cases of anuria have been observed in which the degree of morphologic change was much less than that expected from the clinical state of the patient. A great deal remains to be done in the study of the morphology of acute renal failure. This is an especially fertile area for electron microscopy.

Interstitial Changes

Clinically significant processes involving the stroma usually also produce changes in both the parenchyma and the pelvis. Many of the changes that result in renal impairment are progressive for long periods and have few signs and symptoms. Significant pyelonephritis is found in up to 10 per cent of autopsy cases. In Smithwick's series of 1,251 biopsies between 1946 and 1955, 13 per cent were interpreted as showing pyelonephritis and this number was thought to be a conservative estimate.[20] In a study by Kipnis et al.[21] a small number of cases showed a good correlation between pathologic changes and renal function. Kark and co-workers[17] have shown that cases not suspected of having pyelonephritis can be diagnosed by renal biopsy and the organism may be isolated by culture from the biopsy needle.

In the cases of familial nephritis that have come to autopsy the end-stage kidneys have been interpreted as characteristic of pyelonephritis.[22]

Because of the focal nature of the pathologic change in chronic pyelonephritis, a negative biopsy does not furnish conclusive evidence against the existence of chronic pyelonephritis nor does a positive finding on renal biopsy eliminate another underlying process.

Summary

The renal biopsy is undoubtedly a justifiable diagnostic tool though it has not yet reached full maturity in clinical practice.

Risks. For most patients the risks do not appear to be excessive. An added caution must be exercised in malignant hypertension but even here after careful appraisal of this added risk the biopsy may still be justified. The experience of the operator would appear to modify some of the risk.

Returns. The biopsy has often added to the confusion surrounding a given case because it may be uninterpretable or because it provides an unfamiliar complex of findings. This result is becoming less common with increasing experience.

Even when the histology of the kidney is not diagnostic, it may suggest something of clinical value about the nature of the disease process, such as the presence of vascular disease, focal nephritis, or tubular disease of unidentified nature. The use of the electron microscope has extended the range of the percutaneous biopsy considerably. It is unfortunate that the cost and complexity of this instrument have confined it to certain centers.

It should be remembered also that a number

of technical failures will occur, and the sampling error may be large.

Despite these real problems, the percutaneous renal biopsy is often the only way of establishing a diagnosis and makes its greatest contribution in the appraisal of the asymptomatic patient with proteinuria and an abnormal urinary sediment.

Summario in Interlingua

Biopsia renal es sin dubita un justificabile methodo diagnostic, ben que illo ha non ancora attingite su complete maturitate in le practica clinic.

Riscos. In le majoritate del patientes le riscos non pare esser excessive. Attention special es indicate in casos de maligne hypertension, sed mesmo hic un meticulose evaluation del risco additional arriva possibilemente al conclusion que le biopsia es justificate. Il pare que le riscos se attenua con le crescente experientia del operante.

Resultatos. Il ha occurrite frequentemente que le biopsia augmentava le confusion in un caso particular proque illo esseva ininterpretabile o proque illo presentava un complexo infamiliar de constatationes. Iste situation deveni minus commun con le crescente experientia del investigatores.

Mesmo si le constatationes reno-histologic non es diagnostic, illos pote suggerer aspectos de interesse clinic con respecto al natura del processo morbide: per exemplo le presentia de morbo vascular, de nephritis focal, o de morbo tubular de natura occulte. Le uso del microscopio electronic ha grandemente extendite le applicationes de biopsia percutanee. Il es infelice que le costo e le complexitate de iste instrumento ha resultate in le restriction de su a certe centros.

On debe expectar le occurrentia de malsuccessos technic, e etiam le margine de error causate per le obtention del specimen pote esser grande.

In despecto de iste problemas (que es real), le percutanee biopsia renal es frequentemnte le sol methodo possibile pro establir le diagnose. Illo face su plus grande contribution in le evaluation del patiente asymptomatic con proteinuria e un anormal sedimento urinari.

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Blount, S. G., Jr., Munyan, E. A., Jr., and Hoffman, M. S.: Hypertrophy of the Right Ventricular Outflow Tract. A Concept of the Electrocardiographic Findings in Atrial Septal Defect. Am. J. Med. **22**: 784 (May), 1957.

The electrocardiograms of 50 normal children and of patients with pulmonic stenosis, atrial septal defect, and mitral stenosis were studied to determine the frequency of the rSr′ pattern in normal children and to determine factors that might yield the rSR′ complex with QRS duration 0.08 to 0.10 second found in certain cardiac defects. Forty-nine of 50 normal children revealed rSr′ in at least 1 right chest lead. Direct leads from the epicardial surface of the right ventricle in 5 patients with atrial septal defects showed rSR′ or rSR′s′ localized beneath the pulmonary valve. Intracavitary electrocardiograms studied during withdrawal of the catheter showed a splintered complex of the delay R-wave variety in the region of the right ventricular outflow tract. In 5 of 8 patients, following surgical correction of valvular pulmonic stenosis, the lead V3R changed to rsR′ pattern. The electrocardiographic changes seen following closure of atrial septal defects were variable. Of 10 patients with mitral stenosis who showed electrocardiographic evidence of right ventricular hypertrophy before surgery, 4 exhibited changes following surgery from a RS pattern to an rSR′ pattern. The evidence is interpreted as supporting the concept that the rSR′ pattern with QRS time of 0.08 to 0.10 second is due to hypertrophy of the right ventricular outflow tract.

Kurland

ABSTRACTS

Editor: STANFORD WESSLER, M.D.

BLOOD COAGULATION AND THROMBOSIS

Anderson, M. C., and Shields, T. W.: Significance of Fatal Pulmonary Embolism in Immediate Postoperative Period. J.A.M.A. **167:** 422 (May 24), 1958.

In a 10 year period, pulmonary embolism was demonstrated in 118 of 943 autopsies on adults. Fatal pulmonary embolism occurred in 22 patients postoperatively. Four of these died in the 24 hours following operation. In these patients a low grade fever and tachycardia associated with reduced physical activity (at least 1 week of hospital confinement prior to surgery) were noted. This combination of fever, tachycardia, and activity restriction, and fatal pulmonary embolism suggested that thrombosis was present prior to surgery. Patients with activity restriction, fever, and tachycardia should be regarded with suspicion of thrombosis, and preoperative prophylaxis is of equal importance to postoperative prophylactic care.

KITCHELL

HYPERTENSION

Bachmann, K. and Bär, C. G.: Experimental and Clinical Results of the Hypotensive Action of Ganglionic Blocking Agents and Rauwolfia Alkaloids. Ztschr. Kreislaufforsch. **47:** 699 (Aug.), 1958.

Thirty-eight patients with malignant hypertension, who did not react to other antihypertensive drugs, were given 10 mg. of camphidonium, 0.2 mg. of reserpine, and 1 mg. of serpentine once a day for 3 to 4 weeks. It was found that the hypotensive effects of camphidonium and reserpine were additive, so that the combined use of both drugs allows smaller doses of the ganglionic blocking agent to be used, resulting in less unwanted side effects. Serpentine was shown to increase cardiac output and to decrease peripheral resistance. Addition of serpentine to camphidonium and reserpine prevents major orthostatic hypotension, which ordinarily results from ganglionic blocking agents, and thus allows ambulant treatment with these agents.

LEPESCHKIN

Fregly, Melvin J.: Effects of Propylthiouracil on Development and Maintenance of Renal Hypertension in Rats. Am. J. Physiol. **194:** 149 (July), 1948.

Dietary treatment of rats with propylthiouracil (PTU) prevented the development of elevated blood pressure usually accompanying kidney encapsulation with latex envelopes. Within 4 weeks after dietary administration, PTU also reduced to control levels the elevated blood pressure of rats whose kidneys were encapsulated 9 weeks previously. With regard to dosage, 0.1 per cent PTU appeared to be more effective than 0.06 per cent. This drug (0.1 per cent) also reduced the blood pressure of normal rats. When PTU was administered to growing rats, body weight remained at the level at which administration began. Older rats generally lost weight on the drug, although the extent of weight loss was not consistent among 3 separate lots of PTU used. The reduction in blood pressure of the "encapsulated" rats could not be attributed solely to the weight loss produced by administration of PTU.

WENDKOS

Girerd, R. J., Rassaert, C. L., Di Pasquale, G., and Kroc, R. L.: Production of Experimental Hypertension and Cardiovascular-Renal Lesions With Licorice and Ammoniated Glycyrrhizin. Am. J. Physiol. **194**: 241 (Aug.), 1958.

The intragastric administration of either licorice or ammoniated glycyrrhizin for 50 days to male rats, unilaterally nephrectomized and given 0.87 per cent sodium chloride solution to drink, caused a blood pressure elevation consistently higher than that induced by desoxycorticosterone acetate (DCA) under similar conditions. Renal and cardiovascular lesions, consisting essentially of arteriolar necrosis and hyalinization, were very severe in the DCA and licorice-tereated groups, while they were milder in the glycyrrhizin group. Licorice or DCA treatment caused a significant polydipsia and growth impairment, whereas the curves of fluid intake and body growth of the glycyrrhizin-treated group remained approximately like those of the controls. These results support some previous reports on the steroid-like activity of licorice. It seems that the hypertensive properties of licorice could be attributed to its glycyrrhizin content, while polydipsia and some other effects may be due to other constituents.

WENDKOS

METABOLIC EFFECT ON CIRCULATION

Weisberg, J., and Rodbard, S.: Distribution of Glycogen in the Rat Heart. Am. J. Physiol. **193**: 466 (June), 1958.

The total and trichloracetic acid soluble fractions of glycogen were determined in various portions of the rat heart. The amount in each portion was compared on the basis of the nitrogen content of the same sample. The total glycogen concentration was highest in the atria, lowest in the left ventricle, and intermediate in the septum and right ventricle. A similar distribution was found for the trichloracetic acid soluble glycogen. The possible role of glycogen in cardiac energetics and structure is discussed.

WENDKOS

imeone, F. A., Husni, E. A., and Weidner, M. G., Jr.: The Effect of l-Norepinephrine Upon the Myocardial Oxygen Tension and Survival in Acute Hemorrhagic Hypotension. Surgery **44**: 168 (July), 1958.

The oxygen tension in the myocardium of 19 dogs was recorded by means of the platinum polarograph during and following a period of rapid systemic arterial bleeding. The oxygen tension of the myocardium fell sharply with the fall in blood pressure, rose promptly with the rise of blood pressure when l-norepinephrine was injected intravenously, fell again when the l-norepinephrine was discontinued and returned nearly to the control levels when the reservoir blood was transfused. In 3 animals, a brief drop in blood pressure preceded the rise in myocardial oxygen tension when the l-norepinephrine was injected. Survival experiments were conducted in 17 pairs of dogs. Each pair was bled rapidly at the same time. One animal received a constant infusion of l-norepinephrine beginning 5 minutes or less after the start of bleeding and severe hypotension and the other served as a control. Animals surviving 2 hours were transfused and returned to their cages and were subsequently autopsied 7 days later. Only 2 of the 17 treated animals died and these before the end of 2 hours of the experiment. Eleven of the 17 untreated controls succumbed, 7 during the 2 hours of the experiment and 4 within the next 12 hours. These experiments indicate that l-norepinephrine corrected the myocardial ischemia which occurred during severe hypotension from bleeding and increased the chances of survival provided it was given less than 5 minutes from the beginning of severe hypotension. There was other evidence to suggest that if administered 10 minutes or longer after the onset of severe hypotension, l-norepinephrine did not have a beneficial effect and might be injurious.

BROTHERS

PHARMACOLOGY

Hall, K. D., and Norris, F. H., Jr.: Fluothane Sensitization of Dog Heart to Action of Epinephrine. Anesthesiology **19**: 631 (Sept.-Oct.), 1958.

The role of Fluothane, a potent, volatile, nonexplosive anesthetic agent, was studied in epinephrine-induced arrhythmias of the dog heart. The dogs were divided into 4 groups: (1) 9 dogs received an average total dose of 74 mg. per Kg. of thiopental over an average period of 313 minutes, forty-two minutes after the drip was stopped Fluothane was started; (2) 17 dogs were given minimal thiopental, maintained on open drop Fluothane and then tested with intravenous epinephrine; (3) 7 dogs were given intramuscular doses of epinephrine or norepinephrine after the arrhythmic threshold for intravenous doses were determined; (4) 11 dogs were treated as in (2), then the respiratory pump was turned on, and the dogs were passively hyperventilated. The Fluothane concentration was reduced and the trials with intravenous epinephrine were carried out. The results showed that Fluothane increased the sensitivity of the dog heart to the effect of epinephrine and norepinephrine. Under similar

conditions, thiopental did not. Intramuscular epinephrine and norepinephrine produced serious, but never fatal, arrhythmias in dogs under Fluothane anesthesia. It required 159 times the intravenous dose to produce a similar effect by intramuscular injection. There does not seem to be an absolute contraindication to using Fluothane and epinephrine in normal, healthy patients, but it is suggested that epinephrine be omitted in the presence of cardiovascular disease.

RINZLER

Harris, A. S., Toth, L. A., and Hoey, T. E.: Arrhythmic and Antiarrhythmic Effects of Sodium, Potassium, and Calcium Salts and of Glucose Injected into Coronary Arteries of Infarcted and Normal Hearts. Circulation Res. **6**: 570 (Sept.), 1958.

Substances such as 1/6 M sodium lactate, 5 per cent glucose, and Locke's solution, exhibited no ectopic excitatory effect by intracoronary injection in the uninfarcted dog heart. After infarction, the same substances produced high-frequency ventricular tachycardia and fibrillation. It is conceivable that the injected fluid mobilized stagnant extravasated fluid containing substances, that were excitatory to live tissue. Application of these observations to the management of infarction when such substances are injected intravenously remains to be explored.

AVIADO

Berne, R. M.: Effect of Epinephrine and Norepinephrine on Coronary Circulation. Circulation Res. **6**: 644 (Sept.), 1958.

The intracoronary administrations of epinephrine and norepinephrine in beating, fibrillating, or potassium-arrested dog hearts indicated that the primary action of both amines was coronary vasoconstriction. Their vasodilator action was secondary to their stimulating effect on myocardial metabolism, particularly to the induced hypoxia of the heart muscle.

AVIADO

Price, H. L., Lurie, A. A., Jones, R. E., Price, M. L., and Linde, H. W.: Cyclopropane Anesthesia. II. Epinephrine and Norepinephrine in Initiation of Ventricular Arrhythmias by Carbon Dioxide Inhalation. Anesthesiology **19**: 619 (Sept.-Oct.), 1958.

The subjects were 28 women who were normal except for complaints judged to necessitate dilatation of the cervix and curettage of the uterus. The ages ranged from 22 to 54 years. The investigation dealt with the effect of hypercarbia on the production of ventricular arrhythmias during cyclopropane anesthesia. Intravenous infusions of epinephrine or norepinephrine at rates of 4 to 26 μg. per minute produced similar arrhythmias in 6 of 8 subjects. The concentration of the amines in arterial plasma during periods of arrhythmias were much greater when the arrhythmias were produced by infusion than when they were caused by hypercarbia, suggesting that an increase in catechol amines was not the cause of arrhythmias. Atropinization did not affect the ability of hypercarbia to initiate ventricular arrhythmias to any extent. Bilateral blockade of the stellate ganglia with a local anesthetic made hypercarbia ineffective in producing ventricular arrhythmias, but did not change the ability of infused amines to do so. The conclusion is that hypercarbia increases the rate of liberation of catechol amines from sympathetic nerves terminating in the myocardium and that this causes ventricular arrhythmias.

RINZLER

PHYSIOLOGY

Mecheikel, L., Nusser, E., and Ulmer, W.: On the Influence of Increased Alveolar CO_2 Pressure on Blood Pressure and Blood Flow in the Systemic and in the Pulmonary Circulation. Ztschr. Kreislaufforsch. **47**: 596 (July), 1958.

The blood flow, the aortic and pulmonary artery pressure, the pressure in the right and left atrium, the ventilatory volume, and the carbon dioxide content of end-expiratory air were recorded in cats under chloralose anesthesia, with open chest and fixed volume of artificial ventilation. In another series of animals, with spontaneous respiration and closed chest, only the pulmonary artery, or the femoral artery pressure, the carbon dioxide content and the ventilatory volume were recorded. In the experiments in artificial respiration, carbon dioxide was added to oxygen; in the series in spontaneous breathing, carbon dioxide was suddenly added or gradually increased by rebreathing. The mean arterial pressure, the effective pressure difference, the resistance, and the 'relative vascular diameter' were calculated from the data recorded. In the animals in artificial, fixed volume respiration, increase in carbon dioxide up to 20 per cent failed to induce hemodynamic changes; only at such carbon dioxide concentration did the pulmonary artery pressure increase in 4 experiments out of 25; the aortic pressure increased in 2 observations. In the animals breathing spontaneously the respiratory volume and the pulmonary arterial pressure increased with the increasing concentration in carbon dioxide; the circulatory effect was probably due to the increased work of respiration. The possible significance of increased carbon dioxide alveolar tension as a regulatory mechanism of alveolar perfusion wa

briefly discussed. It was concluded that the results of acute experiments in the animal cannot be applied to the interpretation of physiopathologic mechanisms in chronic disease in man.

CALABRESI

Knebel, R., and Wick, E.: On the Influence of Respiration on Central Vein Pressure. Ztschr. Kreislaufforsch. **47**: 623 (July), 1958.

In 73 cardiac patients the pressure in the superior vena cava or in the right atrium was recorded synchronously with the intraesophageal pressure: the height of the **a** wave was measured in different phases of respiration; using these data, and adopting the intraesophageal pressure an an estimate of the intrathoracic pressure, the 'transmural' pressure was obtained. Similarly, the pressure in the intra-abdominal inferior vena cava was compared with the intragastric pressure. The velocity of the pulse wave in the venae cavae was also recorded in some cases through a double lumen catheter. It was found that the transmural pressure tracing differed from the atrial or venous pressure directly recorded. In inspiration the filling pressure increased in the intrathoracic superior vena cava and in the right atrium; the intra-abdominal inferior vena cava was constricted by the increased abdominal pressure. These observations support Donder's theory of respiratory suction of blood into the chest. The velocity of the pulse waves increased with the increase in transmural pressure. It was pointed out that these data had been obtained in patients with nearly normal intrathoracic pressure and lying horizontally; the effect of standing and of abnormal intrathoracic pressure was surmised.

CALABRESI

Reynolds, S. R. M., Kirsch, M., and Bing, R. J.: Functional Capillary Beds in the Beating, KCl-Arrested and KCl-Arrested-Perfused Myocardium of the Dog. Circulation Research **6**: 600 (Sept.), 1958.

Arrest of the dog heart by potassium chloride appears to weaken the connective tissue elements so that the myocardial fasciculae may become separated upon fixation. The erythrocytes become swollen and show more rouleaux formation, probably due to the osmotic effect of the potassium chloride solution. The density of erythrocyte-filled capillaries is shifted from the epicardium (in the normal heart) to near the endocardium. Arrest of the heart by potassium chloride for the purpose of yielding a dry field for cardiac surgery makes the heart more sensitive to stress, so that reperfusion of the coronary system at the conclusion of a period of cardiac arrest causes profound tissue hemorrhage.

AVIADO

McKeever, W. P., Gregg, D. E., and Canney, P. C.: Oxygen Uptake of the Nonworking Left Ventricle. Circulation Research **6**: 612 (Sept.), 1958.

In the presence of a normal heart rate, cardiac index, and systemic blood pressure, the oxygen uptake is 8 to 10 ml. per minute per 100 Gm. of left ventricle. In the open chest dog, the corresponding oxygen usages of the left ventricle whose external work has been reduced to zero are as follows: 2 ml. in complete arrest with vagal stimulation or with intracoronary potassium injection; 3.8 ml. in fibrillation; and 3.4 ml. in the empty but beating heart. The experiments with vagal stoppage of the heart lay the groundwork for calculation of the oxygen debt of the heart. A constant finding is the apparent increase in calculated usage of oxygen (1.5 ml.) above the control level immediately after induction of vagal asystole. This increase is believed to be caused by the preceding cardiac activity and could be called oxygen debt.

AVIADO

Wegria, R., Frank, C. W., Wang, H., and Lammerant, J.: The Effect of Atrial and Ventricular Tachycardia on Cardiac Output, Coronary Blood Flow and Mean Arterial Blood Pressure. Circulation Research **6**: 624 (Sept.), 1958.

In anesthetized dogs, electrically induced atrial tachycardia induced a very temporary initial decrease in arterial blood pressure, cardiac output and coronary flow, then a return of all parameters to the control level. Ventricular tachycardia essentially caused the same phenomena but the initial decrease in all 3 measurements was more marked than that of atrial tachycardia of the same rate. The mechanisms underlying these changes were discussed.

AVIADO

Rosenblueth, A.: Functional Refractory Period of Cardiac Tissues. Am. J. Physiol. **194**: 171 (July), 1958.

In dogs anesthetized with pentobarbital, with the heart denervated, the adrenal glands ligated, and the sinoatrial node crushed, pairs of stimuli (S_1-S_2) were applied to the atrium or ventricle, varying the delay between S_1 and S_2. When the atrium was stimulated, the following relations were measured: S_1-S_2:A_1-A_2; A_1-A_2:A_2-V_2; A_1-A_2:V_1-V_2. The corresponding curves for ventricular stimulation were also plotted. Calling R_1 and R_2 the responses at a given site, the S_1-S_1:R_1-R_2 curves usually showed a horizontal branch. This branch indicated that impulses stimulated at different moments in the refractory cycle could reach the recording site at the same moment of the cycle. A theorem is demonstrated which

proves that the constancy of the R_1-R_2 interval cannot be explained merely on the basis of slowed conduction rate of R_2, but implies that the impulse stops at some point in the conducting path. For A-A or V-V propagation, this stop is due to delay in the initiation. For A-V or V-A propagation, the stop occurs at some site in the intermediate conducting tissues. The stop in these cases is due to the existence of a prolonged functional refractory period.

WENDKOS

Heymans, C.: Baroceptor and Chemoceptor Reflexes in Monkeys. Circulation Research **6**: 567 (Sept.), 1958.

Experiments performed on 2 species of monkeys showed that they possess reflex mechanisms similar to those of other mammals. The carotid sinuses are provided with baroceptors that regulate systemic arterial pressure. The adjoining carotid bodies contain chemoceptors that are sensitive to lobeline and cyanide ion, and that induce reflex stimulation of respiration.

AVIADO

Brecher, G. A.: Critical Review of Recent Work on Ventricular Diastolic Suction. Circulation Research **6**: 554 (Sept.), 1958.

It has been postulated by numerous investigators that intraventricular diastolic suction somehow contributes to ventricular filling. This postulate has been based mainly on reasoning from very meager evidence until 1952, when evidence in favor of this concept started to appear. The existence of ventricular diastolic suction has been only established when the ventricle contains a more nearly normal residual volume due to ejection against the resistance of a fluid column. The quantitative contribution of suction to ventricular filling at various residual volumes and various levels of cardiac activity is still unknown.

AVIADO

Denison, A. B., Jr., and Green, H. D.: Effects of Autonomic Nerves and Their Mediators on the Coronary Circulation and Myocardial Contraction. Circulation Research **6**: 633 (Sept.), 1958.

Coronary blood flows (electromagnetic) and peripheral coronary pressure (distal to occluded descending branch) were measured in anesthetized dogs. Electrical stimulation of the sympathetic cardiac nerves, increased myocardial contraction, as did levarterenol, and caused a slight degree of coronary arteriolar dilatation. Parasympathetic fibers exerted no significant effect, although acetylcholine diminished coronary arteriolar tone.

AVIADO

REVIEWS IN CARDIOVASCULAR DISEASE

Rubin, E. H., and Lubliner, R.: The Hamman-Rich Syndrome: Review of the Literature and Analysis of 15 Cases. Medicine **36**: 397 (Dec.), 1957.

Kantrowitz, A., Greenberger, G., and Hurwitz, A.: Historical Review and Recent Advances in Surgery of the Aorta. Part I. New York State J. Med. **57**: 4001 (Dec. 15), 1957; **Part II.** New York State J. Med. **58**: 69 (Jan. 1), 1958.

Lewis, J. K.: Stokes-Adams Disease. An Account of Important Historical Discoveries. Arch. Int. Med. **101**: 130 (Jan.), 1958.

Parker, B. M., and Smith, J. R.: Pulmonary Embolism and Infarction. A Review of the Physiologic Consequences of Pulmonary Arterial Obstruction. Am. J. Med. **24**: 402 (March), 1958.

Leiter, L.: Renal Tubular Dysfunction in Congestive Heart Failure. Bull. New York Acad. Med. **34**: 143 (March), 1958.

Mudge, G. H.: The Kidney and Potassium. Bull. New York Acad. Med. **34**: 152 (March), 1958.

Friedberg, C. K.: A Critical Appraisal of Anticoagulants for Short-Term and Long-Term Use in the Management of Myocardial Infarction and Systemic Arterial Embolism. Part I. New York State J. Med. **58**: 877 (March), 1958.

Friedberg, C. K.: A Critical Appraisal of Anticoagulants for Short-Term and Long-Term Use in Management of Myocardial Infarction and Systemic Arterial Emblism. Part II. New York State J. Med. **58**: 1303 (April), 1958.

Finland, M.: Current Status on Therapy in Bacterial Endocarditis. J.A.M.A. **166**: 364 (Jan. 25), 1958.

Bain, R. C., Edwards, J. E., Scheifley, C. H., and Geraci, J. E.: Right-sided Bacterial Endocarditis and Endarteritis. A Clinical and Pathologic Study. Am. J. Med. **24**: 98 (Jan.), 1958.

Page, I. H.: Serotonin (5-Hydroxytryptamine): The Last Four Years. Physiol. Rev. **38**: 277 (April), 1958.

Sambhi, M. P., and Zimmerman, H. A.: Progress in the Long-Term Management of Coronary Artery Disease. Arch. Int. Med. **101**: 97 (May), 1958.

Sabiston, D. C., Jr., and Blalock, A.: Physiologi and Anatomic Determinants of Coronary Bloo Flow and Their Relationship to Myocardia Revascularization. Surgery **44**: 406 (Aug.) 1958.

Vacca, J. B., Bussman, D. W., and Mudd, J. G. Ebstein's Anomaly: Complete Review of 10 Cases. Am. J. Cardiol. **2**: 210 (Aug.), 1958.

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Intracardiac Phenomena. In Right and Left Heart Catheterization. *Aldo A. Luisada and Chi Kong Liu.* New York, Grune & Stratton, Inc., 1958, 179 pages, 82 figures. $9.50.

Reflexogenic Areas of the Cardiovascular System. *C. Heymans and E. Neil.* Boston, Little, Brown and Company, 1958, 271 pages, 89 illustrations. $10.00.

Dietary Prevention and Treatment of Heart Disease. *John W. Gofman, Alex V. Nichols, and E. Virginia Dobbin.* New York, G. P. Putnam's Sons, 1958, 243 pages. $3.95.

Milestones in Modern Surgery. *Alfred Hurwitz and George A. Degenshein.* New York, Hoeber-Harper, 1958, 510 pages. $15.00.

Ciba Foundation Symposium. The Cerebrospinal Fluid, Production, Circulation and Absorption. *G. E. W. Wolstenholme and Cecilia M. O'Connors, Editors.* Boston, Little, Brown and Company, 1958, 336 pages, 141 illustrations. $9.00.

Fisiopatologia della cefalea nella ipertensione arteriosa. *F. Sicuteri, R. Monfardini, and M. Ricci.* Pisa, Omnia Medica, 1957, 142 pages.

Electrocardiography. *Michael Bernreiter.* Philadelphia, J. B. Lippincott Company, 1958, 136 pages, 92 figures. $5.00.

Human Blood in New York City. A Study of Its Procurement, Distribution and Utilization. *Committee on Public Health, New York Academy of Medicine.* New York, New York Academy of Medicine, 1958, 147 pages.

Non-Toxaemic Hypertension in Pregnancy. *Norman F. Morris and J. C. McClure Browne.* Boston, Little, Brown and Company, 1958, 243 pages. $8.50.

Arteriopatias oclusivas estudio clinico y terapeutico. *Alberto Maman.* Caracas, Universidad Central de Venezuela Facultad de Medicina, 1958, 235 pages.

Principles of Internal Medicine. Ed. 3. *T. R. Harrison, Raymond D. Adams, Ivan L. Bennett, Jr., William H. Resnik, George W. Thorn, and M. M. Wintrobe.* New York, McGraw-Hill Book Co., Inc., 1958, 1775 pages, 205 figures. $18.50.

Atrial Arrhythmias, Digitalis and Potassium. *Bernard Lown and Harold D. Levine.* New York, Landsberger Medical Books, Inc., 1958, 222 pages, 53 figures. $6.90.

Das Serumeiweissbild. *Guido Riva.* Bern, Verlag Hans Huber, 1958, 631 pages. Fr./DM 58.- ($14.50).

The Esophagus. Medical and Surgical Management. *Edward B. Benedict and George L. Nardi.* Boston, Little, Brown and Company, 1958, 390 pages, 108 figures. $15.00.

La Médiastin et sa Pathologie. *M. Bariéty and C. Coury.* Paris, Masson et Cie, 1958, 854 pages, 312 figures. 11.000 fr.

Die Herzinsuffizienz in der Praxis. *Kurt Bloch.* Stuttgart, Georg Thieme Verlag, 1958, 216 pages. DM 19.80 - $(4.70).

Primer Symposium Internacional Sobre Fiebre Reumatica. *Ignacia Chávez.* Mexico, Instituto Nacional de Cardiologia, 1958, 530 pages.

Metabolic Disturbances in Clinical Medicine. *G. A. Smart.* Boston, Little, Brown and Company, 1958, 358 pages. $10.00.

Ciba Foundation Symposium. Neurological Basis of Behaviour. *G. E. W. Wolstenholme and Cecilia M. O'Connor, Editors.* Boston, Little, Brown and Company, 1958, 400 pages. $9.00.

Cardiovascular Collapse in the Operating Room. *Herbert E. Natof and Max S. Sadove.* Philadelphia, J. B. Lippincott Company, 1958, 197 pages. $6.00.

Ciba Foundation Colloquia on Ageing. Water and Electrolyte Metabolism in Relation to Age and Sex. *G. E. W. Wolstenholme and Cecilia M. O'Connor, Editors.* Boston, Little, Brown and Company, 1958, 327 pages. $8.50.

The Care of the Geriatric Patient. *E. V. Cowdry.* St. Louis, C. V. Mosby Co., 1958, 438 pages. $8.00.

What We *Do* Know About Heart Attacks. *John W. Gofman.* New York, G. P. Putnam's Sons, 1958, 180 pages. $3.50.

The Chemical Prevention of Cardiac Necroses. *Hans Selye.* New York, The Ronald Press Company, 1958, 235 pages. $7.50.

Cerebral Vascular Diseases. Transactions of the Second Conference Held under the Auspices of The American Heart Association, Princeton, New Jersey, January 16-18, 1957. *Irving S. Wright, Chairman, Clark H. Millikan, Editor.* New York, Grune & Stratton, Inc., 1958, 224 pages. $4.00.

Advances in Electrocardiography. *Charles E. Kossman.* New York, Grune & Stratton, Inc., 1958, 280 pages, illustrated. $9.75.

Men, Molds, and History. *Félix Martí-Ibáñez.* New York, MD Publications, Inc., 1958, 114 pages. $3.00.

Essentials of Therapeutic Nutrition. *Solomon Garb.* New York, Springer Publishing Co., 1958, 147 pages. $2.00.

Centaur: Essays on the History of Medical Ideas. *Félix Martí-Ibáñez.* New York, MD Publications, Inc., 1958, 714 pages. $6.00.

The Operation. *Leonard Engel.* New York, McGraw-Hill Book Company, Inc., 1958, 277 pages. $4.95.

Equinococosis Cardiaca. *Eduardo J. Canabal, Jorge Dighiero, César V. Aguirre, José M. Baldomir, Joaquin Purcallas, Carlos V. Suzacq, José O. Horjales, Jacobo Hazan, and Pablo S. Algorta.* Montevideo, Imprenta Nacional, 1957, 245 pages.

A Doctor Speaks His Mind. *Roger I. Lee.* Boston, Little, Brown and Company, 1958, 120 pages. $3.00.

Differentialdiagnose innerer Krankheiten. Eine kurzgefasste Darstellung für Ärzte und Studierende. *Robert Hegglin.* Stuttgart, Georg Thieme Verlag, 1959, 819 pages, 517 figures. DM 79.50 - $18.35.

Lipidoses. Diseases of the Intracellular Lipid Metabolism. Ed. 3. Siegfried K. Thannhauser. New York, Grune & Stratton, Inc., 1958, 600 pages, 126 figures. $19.75.

AMERICAN HEART ASSOCIATION, INC.

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$1,531,343 ALLOCATED BY AHA TO SUPPORT 179 INVESTIGATORS

A total of $1,531,343 has been allocated through the national research program of the American Heart Association to support 179 research investigatorships and fellowships during the fiscal year beginning July 1, 1959. Still to be awarded are grants-in-aid for research projects, which will be announced later this year. The Association and its state and local affiliates jointly support the national research program.

This year's allocations provide for six Career Investigators, 72 new and continued Established Investigators, 10 new and continued Established Investigator-Grantees, 45 new and continued Advanced Research Fellows and 46 new and continued Research Fellows.

The sum awarded for investigatorships this year, largest in the Association's history, represents an increase of approximately $100,000 over the sums awarded last year exclusive of Grants-in-Aid. In the current 1958-59 fiscal year, it is estimated that the combined research allocations of the American Heart Association and its affiliates and chapters will reach an all-time high of approximately $8,500,000. With the new 1959-60 allocations, the total sum channeled into scientific research by the Association and its affiliates will stand at over $40,000,000. A complete list of recipients of research awards appears at the end of this section.

AHA SCIENTIFIC SESSIONS TO PRESENT VARIED PROGRAM

The 32nd Annual Scientific Sessions of the American Heart Association will be held this year from Friday, October 23 through Sunday, October 25 at the Trade and Convention Center in Philadelphia.

During the three-day period, sessions on clinical cardiology are scheduled to be held simultaneously with special programs in various subspecialties of the cardiovascular diseases. The Committee on Scientific Sessions Program is planning sessions this year which will integrate the contributions of the basic sciences, clinical experiences, and medical care problems in certain fields of cardiology.

The Association's Council on Arteriosclerosis, formerly the American Society for the Study of Arteriosclerosis, will conduct a symposium and participate in a scientific session. The Council on Arteriosclerosis also has sched-

ABSTRACTS OF PAPERS DUE JUNE 12 FOR AHA SESSIONS

Official forms for the submission of abstracts may now be obtained by those wishing to present *papers* at the annual Scientific Sessions of the American Heart Association, October 23-25 in Philadelphia. Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must be limited to 250 words or less and should contain a brief digest of the results obtained and the conclusions reached. Applications will be screened by the Association's Committee on Scientific Sessions Program.

Forms for submitting abstracts and applications for *scientific* exhibit space may be obtained from Dr. F. J. Lewy, Assistant Medical Director, American Heart Association. They must be returned postmarked no later than June 12, 1959. Space for *industrial* exhibits may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, N.Y.

uled an independent Council meeting in November in Chicago.

Following the Scientific Sessions, the 35th Annual Meeting of the Assembly, delegate body representing all program interests and geographic areas of the Association, will be held in Philadelphia's Bellevue Stratford Hotel, October 26-27.

HIGH BLOOD PRESSURE COUNCIL PROCEEDINGS ON HYPERTENSION PUBLISHED BY ASSOCIATION

The proceedings of the Annual Meeting of the Association's Council on High Blood Pressure Research which met in November 1958, have been published and are now available through local Heart Associations or through the American Heart Association, 44 East 23rd Street, New York 10, N. Y., at $2.50 a copy. A special rate of $2.00 a copy will be given for orders received before May 15, 1959.

Among the scientific presentations and discussions included in the volume are: "*Vascular Responsiveness with Particular Reference to Chlorothiazide,*" by Edward D. Freis, M.D.; "*Labor Force of a Chicago Utility Corporation,*" by Jeremiah Stamler, M.D.; "*The Framingham Study,*" by Abraham Kagan, M.D.; "*Oxidase Inhibitors with Central and Peripheral Neurohumoral Agents,*" by Bernard B. Brodie, Ph.D.; "*The Hemodynamics in Labile Hypertension,*" by Robert H. Rich, M.D., Richard J. Peters, M.D., and Richard H. Lyons, M.D.; and "*Could Hardening of the Arteries Produce Diastolic Hypertension?*" by James Conway, M.D.

The volume, seventh in a series on hypertension based on the Council's annual meetings, also contains lay presentations on the subjects of "*Hypertension and Humanity,*" and "*Coronary Heart Disease—A Panel Discussion.*" The Proceedings were edited by Floyd R. Skelton, M.D., Ph.D., Director, The Urban Maes Research Foundation, Louisiana State University Medical School, New Orleans. Still obtainable at a group price of $6.00 are volumes two, four, five and six, covering the years 1953 and 1955-7.

CONGENITAL HEART DEFECTS EXPLAINED IN NEW AHA FILM

A new film, "Congenital Heart Defects," which may be used by physicians as a visual aid when addressing lay and paramedical groups, is available from local Heart Associations or from the American Heart Association.

Latest in a series of films on the cardiovascular system and its diseases, "Congenital Heart Defects" explains the underlying physiology of a number of congenital heart defects. Through effective use of animation, the film shows the normal heart's structure and contrasts five common defects that may be helped by surgery. These include patent ductus arteriosus, coarctation of the aorta, valvular pulmonary stenosis, tetralogy of Fallot, and an arterial septal defect.

Earlier films in the series, produced for the American Heart Association and its affiliates by Churchill-Wexler Film Productions, are: "Varicose Veins," "Circulation of the Blood," "High Blood Pressure," "Strokes," and "Coronary Heart Disease." All of the films are 16 mm. and run under 10 minutes.

MICROCIRCULATORY CONFERENCE SCHEDULED IN MARYLAND, MAY 4-5

The Seventh Annual Meeting of the Microcirculatory Conference, based on the theme "Intravascular Phenomena," is scheduled to be held May 4-5 in the Clinical Science Building, National Institutes of Health, Bethesda, Md. The program will include an address by Sir Howard Florey on "Some Properties of Endothelium with Special Reference to the Lymphatics," papers on control of blood flow and exhibits of various in vivo microvascular technics.

Scientists interested in anatomy and physilogy of the small blood vessels and in thrombotic and embolic phenomena are especially invited. For further details contact Dr. B. W. Zweifach, Secretary, 550 First Avenue, New York 16, N. Y. Room reservations may be made through Dr. Murray Brown, The National Institutes of Health, Bethesda 14, Md.

CARDIAC PAPERS PUBLISHED BY N.Y. ACADEMY OF SCIENCE

Papers presented on the subject of "Metabolic Factors in Cardiac Contractibility" at a conference sponsored by the New York Academy of Sciences, March 18-19, 1958, have been printed in the Academy's Annals, Volume 72. The volume is obtainable free of charge to Academy members, or at $3.75 a copy to non-members, from the Academy's offices, 2 East 63rd Street, New York 21, N.Y.

The monograph, by Menard M. Gertler, G.W.E. Plaut, et al., contains papers by physiologists, biochemists, biophysicists, clinicians and physicians revealing their diverse viewpoints on the problem of congestive heart failure. Also available in the Academy's Annals, Volume 65, is "The Electrophysiology of the Heart," at $4.50 a copy.

MEETINGS CALENDAR

April 20-24: American College of Physicians, Chicago. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

May 3: American Federation for Clinical Research, Atlantic City. George E. Schreiner, Georgetown University Hospital, Washington 7, D. C.

May 3-4: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Avenue, New York 16, N. Y.

May 5-6: Association of American Physicians, Atlantic City. Paul B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 26-29: American College of Cardiology, Philadelphia. Philip Reichert, 480 Park Avenue, New York 22, N. Y.

June 3-7: American College of Chest Physicians, Atlantic City. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

June 8-12: American Medical Association, Atlantic City. F. J. L. Blasingame, 535 N. Dearborn Street, Chicago 10, Ill.

August 10-13: National Medical Association, Detroit. John T. Givens, 1108 Church Street, Norfolk, Va.

September 13-17: International College of Surgeons, U. S. Section, Chicago. Ross T. McIntyre, 1516 Lake Shore Drive, Chicago 10, Ill.

September 28-October 2: American College of Surgeons, Atlantic City. Paul R. Hawley, 40 E. Erie Street., Chicago 11, Ill.

October 19-23: American Public Health Association, Atlantic City. B. F. Mattison, 1790 Broadway, New York 19, N. Y.

October 23-27: American Heart Association Annual Meeting and Scientific Sessions, Philadelphia. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

ANNOUNCEMENT INTERNATIONAL SOCIETY OF CARDIOLOGY FOUNDATION

The International Society of Cardiology Foundation was organized in 1957 at the initiative of Dr. Paul D. White for the purpose of encouraging and financing international scientific research. The officers include:

Paul D. White, Boston, President; Ignacio Chavez, Mexico, First Vice President; D. Evan Bedford, London, and Pierre W. Duchosal, Geneva, Second Vice Presidents; Louis N. Katz, Chicago, Treasurer; F. D. Mayer, Chicago, Attorney; and J. Stern, Chicago, Secretary.

Research workers in cardiology, in various countries, have already received substantial support from the Foundation. It is hoped that the program will be continued and expanded to include other qualified investigators. Applications for research support may be made through Dr. White, 264 Beacon Street, Boston, Mass.

The Foundation needs continued financial support to expand its program of cardiovascular research at the international level. It gratefully acknowledges the generous gift from the Finnish Society of Cardiology as well as the efforts of Dr. White in stimulating additional bequests and urges *Circulation* readers to make known the Foundation's needs to those who might be able to contribute to its success.

Pierre W. Duchosal
Second Vice President

Vittorio Puddu
Secretary-General

International Society of Cardiology
24, boulevard des Philosophes
Geneva, Switzerland

ABROAD

July 27-30: Shaio Foundation Symposium on Cardiovascular Diseases, Bogota, Colombia. Alberto Vejarano-Laverde, 43-23 Carrera 13, Bogota-Colombia.

AHA AWARD RECIPIENTS

Following is a list of investigators selected for support during the fiscal year beginning July 1, 1959 by the American Heart Association's Research Committee.

Career Investigators

Coons, Albert H., Harvard University Medical School, Boston.

Lorber, Victor, University of Minnesota Medical School, Minneapolis.

Pappenheimer, John R., Harvard University Medical School, Boston.

Sprinson, David B., Columbia University College of Physicians and Surgeons, New York.

Taggart, John V., Columbia University College of Physicians and Surgeons, New York.

Wannamaker, Lewis W., University of Minnesota Medical School, Minneapolis.

Continued Established Investigators

Abelmann, Walter H., Circulation in disorders of metabolism and the regulatory role of the liver. Boston City Hospital and Harvard Medical School, Boston.

Albrink, Margaret J., Effect of metabolic and nutritional factors on serum lipids. Yale University School of Medicine, New Haven.

Barker, Earl S., Renal physiology, normal and pathological. Hospital of the University of Pennsylvania, Philadelphia.

Beck, William S., Rate behavior in metabolic multienzyme systems. Massachusetts General Hospital, Boston.

Benesch, Reinhold, Role of sulfhydryl and disulfide groups in biological systems. Marine Biological Laboratory, Woods Hole, Mass.

Boyle, Edwin, Jr., Comparative studies in lipoprotein transport and metabolism concerning atherosclerosis in man, monkeys and pigs. Medical College of South Carolina, Charleston.

Brewster, William R., Jr., Hemodynamic and metabolic interrelationships and mechanism of action of the thyroid hormones, sympathoadrenal hormones, and the adrenal cortical steroids. Massachusetts General Hospital, Boston.

Briller, Stanley A., Energetics of the myocardium. University of Pennsylvania School of Medicine, Philadelphia.

Brodsky, William A., Renal and electrolyte metabolism. University of Louisville School of Medicine, Louisville.

Cohn, Mildred, Mechanisms of phosphorylation and phosphate transfer reactions. Washington University School of Medicine, St. Louis.

Combes, Burton, Hepatic metabolism during hepatoportal hemodynamic adjustments. University of Texas Southwestern Medical School, Dallas.

Daly, Marie M., Arterial metabolism in hypertension. Goldwater Memorial Hospital, New York.

DuBois, Arthur B., Gas exchange in the lungs, mechanics of breathing and pulmonary capillary blood flow. University of Pennsylvania Graduate School of Medicine, Philadelphia.

Eckstein, John W., Venomotor responses to circulatory alterations in man. State University of Iowa College of Medicine, Iowa City.

Epstein, Franklin H., Metabolic and circulatory factors affecting the distribution and excretion of water and electrolytes. Yale University School of Medicine, New Haven.

Farber, Saul J., Role of electrolytes and their relationship to extracellular and intracellular organic constituents in heart disease and other diseases producing edema. New York University College of Medicine, New York.

Farrell, Gordon L., Physiological factors which regulate the secretion of aldosterone. Western Reserve University School of Medicine, Cleveland.

Finnerty, Frank A., Jr., Further studies on the pathogenesis of toxemia of pregnancy and other types of acute hypertension. District of Columbia General Hospital, Washington, D. C.

Flavin, Martin, Jr., Enzyme chemistry and intermediary metabolism. National Heart Institute, Bethesda, Md.

Foulkes, Ernest C., Fundamental mechanisms of electrolyte transport across biological membranes. May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Fresco, Jacques R., Macromolecular aspects of nucleic acid structure and function. Harvard University, Cambridge, Mass.

Gamble, James L., Jr., Mitochondrial function in relation to electrolyte transport. Johns Hopkins University School of Medicine, Baltimore.

Gibson, David M., Enzymatic synthesis of fatty acids in animal tissues. Indiana University School of Medicine, Indianapolis.

Gidez, Lewis I., Factors determining serum lipid composition and concentration. Albert Einstein College of Medicine, Yeshiva University, New York.

Giebisch, Gerhard, Ion transport across renal tubules of the amphibian and mammalian kidney, utilizing micropuncture techniques. Cornell University Medical College, New York.

Gilbert, James B., Role and site of binding of the metal ion in metal-containing or metal-activated enzymes. Clayton Foundation, Biochemical Institute, University of Texas, Austin.

Gitlin, David, Blood and tissue proteins. Harvard Medical School, Boston.

Goldthwait, David A., Biosynthesis of purine nucleotides and of ribonucleic acid. Western Reserve University School of Medicine, Cleveland.

Gottschalk, Carl W., Micropuncture study of kidney function. University of North Carolina School of Medicine, Chapel Hill.

Gross, Jerome, Structure, composition, genesis, function and malfunction of connective tissues. Massachusetts General Hospital, Boston.

Havel, Richard J., Mechanisms of lipid transport and the relation of altered lipid transport to atherogenesis. University of California Medical Center, San Francisco.

Huckabee, William E., Metabolic reactions to circulatory disturbances and their role in the control of the circulation. Massachusetts Memorial Hospitals, Boston.

Jacobs, Earl E., Structural factors involved in mitochondrial oxidative phosphorylation mechanisms. Dartmouth Medical School, Hanover, N. H.

Kaplan, Melvin H., Localization of tissue-deposited streptococcal antigens and antibodies in animal and human tissues by means of the fluorescein-labeling technique; pathogenesis of rheumatic fever and rheumatic heart disease in relationship to the autoimmune theory of pathogenesis. Cuyahoga County Hospital, Cleveland.

Katz, Yale J., Renal revascularization in experimental hypertension and renal insufficiency. University of Southern California School of Medicine, Los Angeles.

Kun, Ernest, Pathway of the metabolism of hydroxy acids. University of California Medical Center, San Francisco.

Kuo, Peter T., Intravascular distribution of lipid particles in clinical arteriosclerosis. Hospital of the University of Pennsylvania and University of Pennsylvania School of Medicine, Philadelphia.

Lazzarini, Abel A., Jr., Metabolic and immunological changes occurring in transplanted tissues. New York University Post-Graduate Medical School, New York.

Lewis, David H., Regulation of the circulation in man. Philadelphia General Hospital, Philadelphia.

Linker, Alfred, Mucopolysaccharides. Columbia University College of Physicians and Surgeons, New York.

Mackler, Bruce, Metabolic sequences involved in electron transport in mammalian tissues. University of Washington School of Medicine, Seattle.

Mann, George V., Cause and prevention of atherosclerosis. Vanderbilt University School of Medicine, Nashville, Tenn.

Nelson, Clifford V., I. Mechanism of fibrillation. II. Quantitation of the vectorcardiogram. Maine Medical Center, Portland.

Padawer, Jacques, Physiology of the mast cell and its relation to cardiovascular function and disease. Albert Einstein College of Medicine, Yeshiva University, New York.

Perry, H. Mitchell, Jr., Pathogenesis and treatment of hypertension and atherosclerosis. Washington University School of Medicine, St. Louis.

Pick, Ruth, Pathogenesis of atherosclerosis and its sequelae. Medical Research Institute, Michael Reese Hospital, Chicago.

Richmond, Jonas E., Role of the prosthetic group of proteins in the biosynthesis and metabolism of conjugated proteins. Harvard Medical School, Boston.

Rudolph, Abraham M., Pulmonary hypertension in congenital heart disease. Children's Medical Center, Boston.

Schmidt-Nielsen, Bodil M., Comparative kidney physiology. Duke University, Durham, N. C.

Schwartz, William B., Disorders of electrolyte metabolism and kidney function. New England Center Hospital, Boston.

Schweet, Richard S., Biological synthesis of protein. City of Hope Medical Center, Duarte, Cal.

Sharp, John T., Physical properties of the lungs in pulmonary edema; mechanism of increased pulmonary vascular resistance. University of Buffalo School of Medicine and Buffalo General Hospital, New York.

Slade, Hutton D., Biochemistry of the group A hemolytic streptococcus. Northwestern University Medical School, Chicago.

Spencer, Merrill P., Factors affecting distribution of cardiac output. Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.

Springer, Georg F., Plant polysaccharides in relation to lipemia clearing, coagulation, blood group specificity and infectious mononucleosis. Hospital of the University of Pennsylvania, Philadelphia.

Staple, Ezra, Metabolism of cholesterol, mechanisms of synthesis and breakdown of related substances. University of Pennsylvania School of Medicine, Philadelphia.

Szent-Gyorgyi, Andrew G., Structure of myosin. Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass.

Thal, Alan P., I. Revascularization of the myocardium; experimental study designed to test the feasibility of a direct suture anastomosis of extracardiac arteries to the coronary arteries. II. Mechanism of action of bacteria and bacterial toxins on small blood vessels with particular reference to bacterial shock. University of Minnesota Medical School, Minneapolis.

Ulrich, Frank, Metabolic fate and mechanism(s) of action of adrenal cortical hormones in the peripheral tissues. Yale University School of Medicine, New Haven, Conn.

Walker, W. Gordon, I. Plasma protein metabolism,

capillary protein permeability and circulatory homeostasis. II. Hyponatremia in congestive heart failure. III. Electrolyte permeability in the gut. Johns Hopkins Hospital, Baltimore.

Zweifach, Benjamin W., Histochemical and microchemical analysis of structural elements of blood-tissue barrier. New York University College of Medicine, New York.

New Established Investigators

Bricker, Neal S., Pathological physiology of chronic Bright's disease. Washington University School of Medicine, St. Louis.

Martin, Harry B., Surface tension as a factor in the mechanical properties of normal and abnormal lungs. Harvard University School of Public Health, Boston.

Morgan, Richard S., Ribonucleic acid structures. Brandeis University, Waltham, Mass.

Pollak, Victor E., Investigations on the kidney in health and disease. University of Illinois College of Medicine, Chicago.

Portman, Oscar W., Dietary factors affecting cholesterol catabolism and atherosclerosis. Harvard University School of Public Health, Boston.

Shumway, Norman E., Jr., Ventricular fibrillation by threshold determinations. Stanford University Hospitals and Stanford University School of Medicine, San Francisco.

Straus, Werner, Investigation of "phagosomes" in various tissues of the rat. University of Louvain, Louvain, Belgium.

Travis, Randall H., Hydrocortisone metabolism in diabetes mellitus. University Hospitals of Cleveland and Western Reserve University School of Medicine, Cleveland.

Tsuboi, Kenneth K., Metabolism of nucleotides and related compounds in cardiac tissues. Cornell University Medical College, New York.

Vernier, Robert L., Etiology and pathogenesis of diffuse cardiovascular disease in childhood. University of Minnesota Medical School, Minneapolis.

Warner, Homer R., Application of analogue computer techniques to the study of regulation of the circulation. University of Utah College of Medicine and Latter-Day Saints Hospital, Salt Lake City.

Continued Established Investigator—Grantees

Corcoran, John W., Metabolism of the branched chain monosaccharides and their role in the mammalian and bacterial cell. Western Reserve University School of Medicine, Cleveland.

Durbin, Richard P., Transport of water and HCl by the stomach. Harvard Medical School, Boston.

Goldstein, Robert, Isolation and identification of prothrombin and "serum factors"; investigation of their role in coagulation and thrombosis. New England Center Hospital, Boston.

Henly, Walter S., Determination of myocardial blood flow in the intact subject, utilizing radioiodinated (I^{131}) human serum albumin. Baylor University College of Medicine, Houston.

Khairallah, Philip A., Reactivity of blood vessels. Cleveland Clinic, Cleveland.

Rubin, Albert L., Investigation of the metabolic alterations in the uremic syndrome. Cornell University Medical College and New York Hospital, New York.

New Established Investigator—Grantees

Conway, F. James, Aging of arteries in relation to hypertension. University of Michigan Medical School, Ann Arbor.

Despopoulos, Agamemnon, Parameters of cellular transport phenomena. University of Louisville School of Medicine, Louisville.

Landau, Bernard R., Carbohydrate metabolism in hyperthyroidism. New England Center Hospital, Boston.

Page, Ernest, Ion fluxes in mammalian heart muscle. Harvard Medical School, Boston.

Continued Advanced Research Fellows

Boucot, Nancy G., Alterations in metabolism in renal disease (with preliminary work in intermediary metabolism in the normal animal). Under Eric G. Ball and James Ashmore, Harvard Medical School, Boston.

Brady, Allan J., Myocardial tension related to transmembrane potentials and ion fluxes. Under Wilfried F. H. M. Mommaerts, University of California Medical Center, Los Angeles.

Cheng, Tsung O., Respiratory and circulatory changes during exercise. Under Richard L. Riley, Johns Hopkins University School of Hygiene and Public Health, Baltimore.

Cohn, George L., Formation of an "aldosterone-like" compound by the liver of patients with congestive heart failure after the intravenous administration of cortisol. Under Philip K. Bondy, Yale University School of Medicine, New Haven.

DeWall, Richard A., Perfusion techniques for reparative open intracardiac surgery. Under C. Walton Lillehei, University of Minnesota Medical School, Minneapolis.

Dontas, Anastasius S., Aging of arteries; diagnosis in the human. Epidemiology of atherosclerosis. Under Ancel Keys, University of Minnesota School of Public Health, Minneapolis.

Feinberg, Harold, Investigation of the in vivo metabolism of the myocardium. Under Louis N. Katz, Medical Research Institute, Michael Reese Hospital, Chicago.

Frazier, Howard S., Effect of ouabain on activation in striated muscle. Under Alexander Leaf, Massachusetts General Hospital, Boston.

Gubler, Clark J., Enzymatic functions of thiamine. Under H. Smith Broadbent, Brigham Young University, Provo, Utah.

Harris, John B., In vitro studies of the biochemical and biophysical properties of potassium metabolism. Under Isidore S. Edelman, University of California Medical Center, San Francisco.

Hatch, Frederick T., Biosynthesis of the methyl groups; coenzymatic role of vitamin B_{12}. Under John M. Buchanan, Massachusetts Institute of Technology, Cambridge, Mass.

Hill, Robert, Relationship of diet to lipogenesis and cholesterogenesis. Under I. L. Chaikoff, University of California School of Medicine, Berkeley.

Hirschhorn, Kurt, Metabolic mechanisms in familial hyperlipemia. Under Charles F. Wilkinson, Jr., New York University Post-Graduate Medical School, New York.

Javitt, Norman B., Patterns of proteinuria in chronic renal disease. Under Stanley E. Bradley, Columbia University College of Physicians and Surgeons, New York.

Levitin, Howard, Renal tubular response to respiratory acidosis. Under Franklin H. Epstein, Yale University School of Medicine, New Haven.

Luchsinger, Peter C., Effect of O_2 breathing upon arterial and mixed venous blood gas composition and the hemodynamics of the pulmonary and systemic circulation in the cardiac patient. Under Sol Katz and James J. Leonard, District of Columbia General Hospital, Washington, D.C.

Maley, Gladys F., Biosynthesis of heparin. Under Frank Maley, New York State Department of Health, Albany, N.Y.

Montgomery, A. Vernon, Jr., Genesis and control of ventricular fibrillation. Under Henry Swan, University of Colorado School of Medicine, Denver.

Moskowitz, Merle S., Sexually-controlled factors affecting atherogenesis and coronary thrombosis. Under Robert W. Wissler, University of Chicago School of Medicine, Chicago.

Penniall, Ralph, Adenosinetriphosphatases of heart tissue, with particular emphasis on the enzyme stimulated by 2,4-dinitrophenol. Under J. Logan Irvin, University of North Carolina School of Medicine, Chapel Hill, N.C.

Reichard, Sherwood M., Role of tocopheral in electron transport in the adrenal glands. Under Alvin Nason, McCollum-Pratt Institute, Johns Hopkins University, Baltimore.

Savitsky, J. Philip, Modifying effect of lung protein fractions on experimental lipemia and hypercholesterolemia. Under Louis Leiter, Montefiore Hospital, New York.

Weiss, Arthur J., Kinetics of various coagulation systems. Under William Sodeman, Jefferson Medical College of Philadelphia.

Whereat, Arthur F., Transport mechanisms and metabolic fate of cholesterol. Under Samuel Gurin, University of Pennsylvania School of Medicine, Philadelphia.

New Advanced Research Fellows

Cayler, Glen G., Longitudinal study of hemodynamic and pulmonary vascular changes in the full-term and premature puppy. Under Robert H. Bayley, University of Oklahoma School of Medicine, Oklahoma City.

Dickerman, Herbert W., Purification and mechanism of pig spleen diphosphopyridine nucleotidase. Under Anthony San Pietro, McCollum-Pratt Institute, Johns Hopkins University, Baltimore.

Goodkind, M. Jay, Myocardial metabolism in normal and hyperkinetic states. Under Allan V. N. Goodyer, Yale University School of Medicine, New Haven.

Greenberg, Wayne V., Role of growth hormone in lipid metabolism and atherogenesis. Under Olof H. Pearson, Sloan-Kettering Institute for Cancer Research, New York.

Katz, Joseph, Mechanism and site of plasma protein breakdown. Under Alvin L. Sellers, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles.

Lacy, William W., Metabolism in uremia. Under Elliot V. Newman, Vanderbilt University School of Medicine, Nashville.

Mueller, Helmut, Molecular physiology of the relaxing mechanism in contractile systems. Under S. V. Perry, University of Cambridge, England.

Nathan, Paul, Kidney transplantation. Under Benjamin F. Miller, May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Peifer, James J., Chemistry and metabolism of lipids related to heart disease. Under Walter O. Lundberg, Hormel Institute, University of Minnesota, Austin.

Radding, Charles M., Biochemical basis of genetics. Under Arthur Kornberg, Stanford University School of Medicine, Palo Alto, Cal.

Rakita, Louis, Nature of myocardial hypertrophy; transmembrane potential, intramural potential, and histochemical alterations in myocardial muscle associated with ventricular hypertrophy. Under Charles H. Rammelkamp, Jr., Cuyahoga County Hospital, Cleveland.

Reeves, John T., Oxygen transport and the pulmonary circulation at rest and during exercise in normal and pathological subjects. Under S. Gilbert Blount, Jr., Colorado General Hospital and University of Colorado School of Medicine, Denver.

Ronwin, Edward, Enzymes involved in blood clotting

and their mechanism of action; isolation of indicated clotting reaction intermediates. Under George P. Hager, University of Minnesota College of Pharmacy, Minneapolis.

Rosa, Leslie M., Chest accelerograms and vibrocardiograms in coronary heart diseases. Under Aldo A. Luisada, Chicago Medical School.

Spiro, Robert G., Composition and structure of the carbohydrate moiety of the glycoprotein of fetal calf serum. Under Roger W. Jeanloz, Massachusetts General Hospital, Boston.

Stanfield, Calvin A., Effects of exercise and various pharmacological agents on pulmonary circulation and ventricular function. Under Paul N. Yu and Frank W. Lovejoy, Jr., University of Rochester School of Medicine and Dentistry, Rochester.

Stoffyn, Pierre J., Chemistry and biochemistry of heparin. Under Roger W. Jeanloz, Massachusetts General Hospital, Boston.

Taranta, Angelo, Secondary immune response: reinvestigation. Studies on Sydenham's chorea. Under Harrison F. Wood, Irvington House, Irvington-on-Hudson, N. Y.

Tuna, Naip, Fatty acids and atherosclerosis. Under Ivan D. Frantz, Jr., University of Minnesota Medical School, Minneapolis.

Vance, Vernon K., Adrenal inhibition in edematous states. Under George W. Thorn, Peter Bent Brigham Hospital, Boston.

Welsh, Richard S., Characterization of an undegraded, nonfibrous form of desoxyribonucleoprotein from calf thymus. Under George J. Hollenberg, University of Redlands, Cal.

Continued Research Fellows

Abboud, Francois, Arterial wall elasticity in arteriosclerotic and hypertensive vascular disease. Under John H. Huston, Marquette University School of Medicine, Milwaukee.

Carrasquer, Gaspar, Electrolyte and water function of the kidney; mechanism of tubular ion transport and acidification of the urine. Under William A. Brodsky, University of Louisville School of Medicine, Louisville.

Childers, Roderick W., Emphysema heart; cardiac and pulmonary function. Under David Littman, West Roxbury Veterans Hospital, West Roxbury, Mass.

Choudhury, Jyotirmoy D., Cardiopulmonary physiology. Under Julius H. Comroe, Jr., Cardiovascular Research Institute, University of California Medical Center, San Francisco.

Cohen, Louis, Metabolism of lipoproteins; incorporation and decay of lipid in alpha and beta lipoproteins. Under Emmett Bay and Richard J. Jones, University of Chicago School of Medicine.

Cushing, Ivan E., Jr., Alterations in the mechanics of respiration in patients with pulmonary edema and cor pulmonale in relation to the symptom dyspnea and other aspects of cardiopulmonary function. Under William F. Miller and Carleton B. Chapman, University of Texas Southwestern Medical School, Dallas.

deGroot, William J., I. Alveolocapillary gas exchange in patients with pulmonary hypertension secondary to congenital heart disease. II. Determination of catheter influences on the normal pulmonary valve pressure gradient. Under Sol Katz, James J. Leonard and Peter C. Luchsinger, District of Columbia General Hospital, Washington, D. C.

Derks, Miriam A., Metabolism of pyrimidines and carbamylamino acids. Under Santiago Grisolia, University of Kansas Medical Center, Kansas City.

Dock, Donald S., Clinical and physiological correlations in valvular insufficiency. Under Lewis Dexter, Peter Bent Brigham Hospital, Boston.

Ells, Hugh A., Effects of quinidine on cell permeability and carbohydrate metabolism. Under Robert H. Furman, Oklahoma Medical Research Foundation, Oklahoma City.

Friedberg, Samuel J., Tissue electrolyte studies in hyponatremia. Under E. Harvey Estes, Duke University Hospital and Veterans Administration Hospital, Durham, N. C.

Friedman, Eli A., Immune reaction against homotransplanted tissue in man. Under John P. Merrill, Peter Bent Brigham Hospital, Boston.

Glagov, Seymour, Localization of atheromatous changes as a function of altered circulatory conditions in the supplied organs. Under Donald A. Rowley, University of Chicago School of Medicine.

Grayson, Richard R., Fundamental digitalis research. Under John R. Smith, Washington University School of Medicine, St. Louis.

Harrison, James L., Aortic valve prosthesis. Under Robert P. Glover, Presbyterian Hospital, Philadelphia.

Lauler, David P., I. Analysis of renal function tests. II. Interrelationship of electrolytes and renal dynamics. Under Laurence G. Wesson, Jr., New York University Post-Graduate Medical School, New York.

Manfredi, Felice, Mechanisms of regulation of the pulmonary circulation. Under Herbert O. Sieker, Duke University School of Medicine, Durham, N. C.

Nechay, Bohdan R., Interrelations of diuretic agents. Under Thomas H. Maren, University of Florida College of Medicine, Gainesville.

Oken, Donald E., Renal tubular biophysiology. Under Arthur K. Solomon, Harvard Medical School, Boston.

Rausch, Nancy H., Relationship between cardiovascular and renal responses in patients with hyperkinetic circulatory states. Under Walter E. Jud-

son, Indiana University School of Medicine, Indianapolis.

Rodriguez, Felix L., Qualitative and quantitative vascular injection studies on the heart. Under G. Kenneth Mallory and Stanley L. Robbins, Mallory Institute of Pathology, Boston City Hospital, Boston.

Samuel, Paul, I. Effect of diet rich in unsaturated fatty acids in serum lipids and clinical course of patients with coronary atherosclerosis. II. Effect of diet rich in unsaturated fatty acids in the production of experimental atherosclerosis in rabbits and dogs. Under Charles F. Wilkinson, Jr., New York University Post-Graduate Medical School, New York.

Shabetai, Ralph, Dynamics of cardiac tamponade and paradoxical pulse. Under Noble O. Fowler, Cincinnati General Hospital, Cincinnati.

Shnecour, Elie A., Carotenoid synthesis. Under Roger Y. Stonier, University of California, Berkeley.

Stein, Samuel W., Correlative study of pulmonary diffusion of gases and pulmonary hemodynamics in patients with heart disease. Under Laurence B. Ellis, Boston City Hospital, Boston.

Traks, Elmerice, Effects of heat upon the circulation of man. Under Salvatore M. Sanoetta, Cuyahoga County Hospital, Cleveland.

Yaffe, Sumner J., Enzyme studies of the human kidney. Under Charles A. Janeway, Children's Hospital, Boston.

New Research Fellows

Baskys, Bronius, In vitro studies of the effects of various lipases on the serum lipoproteins in normal individuals and in patients with idiopathic hyperlipemia and primary hypercholesteremia. Under Walter F. Lever, Massachusetts General Hospital, Boston.

Constantine, Herbert P., Diffusion capacity of the lung and its relationship with the pulmonary circulatory dynamics. Under Nolan Kaltreider and Paul N. Yu, University of Rochester Medical Center, Rochester, N. Y.

Cooke, C. Robert, "Stop-flow" investigation of renal function in man. Under W. Gordon Walker, Johns Hopkins Hospital, Baltimore.

Corn, Milton, Aspects of antigen-antibody reaction involving blood platelets of humans and dogs. Under C. Lockard Conley, Johns Hopkins Hospital, Baltimore.

Erb, Blair D., Clinical evaluation of selective cardiac plethysmography, using the radio-frequency impedance technique. Under Daniel A. Brody, University of Tennessee School of Medicine, Memphis.

Fekete, Laszlo L., Relation of inhibition of lipemia clearing to disturbed lipid transport. Under Walter F. Lever, Massachusetts General Hospital, Boston.

Griege, Charles W., Coronary circulation and cardiac metabolism in normal and pathological conditions. Under René Wégria, Saint Louis University School of Medicine, St. Louis.

Hays, Richard M., Maintenance of an asmotic gradient across a living membrane. Under Alexander Leaf, Massachusetts General Hospital, Boston.

Levine, Herbert J., Coronary circulation in health and disease. Under Richard Gorlin, Harvard Medical School, Boston.

Levy, Joseph V., Physiology and pharmacology of the mammalian S-A node. Under Theodore C. West, University of Washington School of Medicine, Seattle.

MacLeod, Robert M., Relationships of cell structure to cell function. Under William S. Lynn, Duke University School of Medicine, Durham, N. C.

Miller, Tracy B., Nature of the primary process responsible for sodium and chloride reabsorption by renal tubule cells using nitrate-loaded dogs undergoing mercurial diuresis. Under Alfred E. Farah, State University of New York Upstate Medical Center, Syracuse.

Morrin, Peter A. F., Pathological physiology of Bright's disease. Under Neal S. Bricker, Barnes Hospital, St. Louis.

Peters, John H., Role of immune mechanisms in the etiology and pathogenesis of renal disease. Under Albert H. Coons, Harvard Medical School, Boston.

Pierucci, Louis, Jr., Studies of extracorporeal circulation. Under John H. Gibbon, Jr. and J. Y. Templeton III, Jefferson Medical College, Philadelphia.

Shalhoub, Robert J., Site of direct action of cardiac glycosides on sodium reabsorption in the dog kidney. Under Robert F. Pitts, Cornell University Medical College, New York.

Utley, James H., Turnover and uptake of nonesterified fatty acids by the heart. Under Richard J. Bing, Washington University School of Medicine, St. Louis.

Warwick, Warren J., Delayed type bacterial allergy. Under Robert A. Good, Heart Hospital and University of Minnesota Medical School, Minneapolis.

Williams, John F., Jr., Cardiac response of patients with pulmonary emphysema to exercise and venesection. Under Roy H. Behnke, Veterans Administration Hospital and Indiana University Medical Center, Indianapolis.

CONTRIBUTORS TO THIS ISSUE

W. Wyman Andrus, M.D.
Clinical Associate, School of Medicine, University of Washington, Seattle, Wash.

Aurora Maria Antonio, M.D.
Resident, New York University Research Service at Goldwater Memorial Hospital, New York, N. Y.

John D. Arnold, M.D.
Associate Professor of Medicine, University of Chicago Medical School, Chicago, Ill.

William H. Bernstein, M.D.
Attending Physician, Department of Medicine, Mt. Sinai Hospital, Miami Beach, Fla.

Aurelius Bogdanovitz, M.D.
Former Trainee of the New York Heart Association.

Warren S. Braveman, M.D.
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Robert A. Bruce, M.D.
Associate Professor of Medicine, School of Medicine, University of Washington, Seattle, Wash.

Francis S. Caliva, M.D.
Assistant Professor of Medicine, Upstate Medical Center, State University of New York, Syracuse, N. Y.

Waddy Chapman, M.D.
Assistant Resident in Pathology, Medical College of South Carolina, Charleston, S. C.

Leonard A. Cobb, M.D.
Instructor in Medicine, School of Medicine, University of Washington, Seattle, Wash.

Burton D. Cohen, M.D.
Research Fellow, Cornell University Medical College, 1957-1958; Presently Resident in Medicine, Memorial Center for Cancer and Allied Diseases and Instructor in Medicine, Cornell University Medical College, New York, N. Y.

Harold P. Collins, M.D.
Fellow in Cardiovascular Surgery, Baylor University College of Medicine, Houston, Tex.

Denton A. Cooley, M.D.
Associate Professor of Surgery, Baylor University College of Medicine, Houston, Tex.

James H. Currens, M.D.
Assistant in Medicine, Massachusetts General Hospital; Associate Physician, Boston Lying-In Hospital, Boston, Mass.

David C. Daniels, B.S.
Medical Student, Ohio State University College of Medicine, Columbus, Ohio.

Kurt De Crinis, M.D.
Research Fellow, New York University College of Medicine; Resident, New York University Research Service at Goldwater Memorial Hospital, New York, N. Y.

E. E. Eddleman, Jr., M.D.
Associate Professor of Medicine, Medical College of Alabama, and Chief of Medicine, Veterans Administration Hospital, Birmingham, Ala.

Frederic Eldridge, M.D.
Assistant Professor of Medicine, Stanford University School of Medicine, San Francisco, Calif.

Eugene M. Fierer, M.D.
Research Fellow, Cardio-Pulmonary Laboratory, Mt. Sinai Hospital, Miami Beach, and Research Fellow of the Division of Cardiology of the Department of Medicine, University of Miami School of Medicine, Coral Gables, Fla.

George W. Frimpter, M.D.
Research Fellow, National Heart Institute, Department of Medicine, Cornell University Medical College, New York, N. Y.

Theodore J. Fuller, M.D.
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